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THE UNIVERSITY OF ALBERTA

STUDIES ON THE CHEMISTRY AND PHARMACOLOGY OF REDUCED PYRIDINES

by

BRENT K. WARREN

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "Studies on the Chemistry and Pharmacology of Reduced Pyridines" submitted by Brent K. Warren in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences (Medicinal Chemistry).

DEDICATION

To My Family

"It is doubted whether a man ever brings his facilities to bear with their full force on a subject until he writes upon it."

Cicero

ABSTRACT

The 1,3-dipolarcycloaddition reaction of cyanogen- and sulfonyl azides with 1-methyl-1,4-dihydropyridine (XLIII) afforded 2-methyl-7-cyano(sulfonyl)-2,7-diazabicyclo[4.1.0]-hept-3-enes in excellent yield. The 2,7-diazabicyclo[4.1.0]-hept-3-enes displayed good antiprotozoal and analgesic activities.

In a similar manner, 1-alkyl-1,2,3,4-tetrahydropyridines undergo a 1,3-dipolarcycloaddition reaction with cyanogen- and sulfonyl azides to give 1-alkylpiperidylidene-2-cyan(sulfon)amides. Acid hydrolysis of 1-methylpiperidylidene-2-cyanamide yielded 1-methyl-2-piperidone. The 1-methylpiperidylidene-2-sulfonamides have excellent analgesic properties which are antagonized by Naloxone hydrochloride, a narcotic antagonist. The most potent analgesic prepared was 1-[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide which is 10,000 fold more active than morphine sulfate in mice. Narcotic analgesic agonist-antagonist properties were displayed by 1-cycloalkylmethyl(*n*-propyl, isobutyl)piperidylidene-2-(4-chlorophenyl)sulfonamides. It is likely that 1-methylpiperidylidene-2-sulfonamides (CLXXV) are narcotic analgesics acting at the μ-narcotic opiate receptor while the 1-cycloalkylmethyl(larger alkyl)-piperidylidene-2-sulfonamides are μ-receptor antagonists and κ-receptor agonists. Structure-activity relationships

indicate that CLXXV has many structural features in common with typical narcotic analgesics.

The reaction of 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates with sodium borohydride affords 3-methyl-10-dialkylaminoalkyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazines (CC, CCIII, CCV, CCVII, CCIX). Subsequent treatment of these 1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazines with 10% palladium on charcoal and hydrogen gas yields 3-methyl-10-dialkylaminoalkyl-10H-1,1a,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazines (CCII, CCIV, CCVI, CCVIII, CCX). The tetra(hexa)hydropyrido-[3,4-b][1,4]benzothiazines displayed mild analgetic properties.

Reaction of 10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine with n-butyllithium and deuterium oxide affords 4-deutero-10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVII) and 4-n-butyl-10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVIII). A mechanism for the formation of CCXVII and CCXVIII is given.

Treatment of 10H-pyrido[3,4-b][1,4]benzothiazine with diisobutylaluminum hydride (DIBAH) and methyl chloroformate or the reagents borane-tetrahydrofuran, sodium bis-(2-methoxyethoxy)aluminum hydride and methyl chloroformate gave 10-methoxycarbonyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXXI) and bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b]-[1,4]benzothiazine (CCXXII). Reaction of a 10-dialkylamino-

alkyl-10H-pyrido[3,4-b][1,4]benzothiazine with DIBAH and methyl chloroformate gave only intractable material. Compound CCXXII exhibits good analgesic properties.

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LIST OF ABBREVIATIONS

bp	- boiling point
cm	- centimeter
CI	- chemical ionization
°C	- degrees Celcius
$CDCl_3$	- deuterochloroform
DIBAH	- Diisobutylaluminium hydride
DMSO-d_6	- hexadeuterodimethyl sulfoxide
EI	- electron impact
ED_{50}	- exact 50% effective dose
g	- gram
h	- hour
ir	- infrared spectrum
LD_{50}	- exact 50% lethal dose
ms	- mass spectrum
mm	- millimeter
mp	- melting point
mg	- milligram
mL	- milliliter
mmol	- millimole
min	- minute
mol	- mole
nmr	- ^{1}H magnetic resonance
Redal	- Sodium bis(2-methoxyethoxy)aluminum hydride
psi	- pounds per square inch
sec	- second
sc	- subcutaneous
tlc	- thin layer chromatography

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1.0.0.0.0 INTRODUCTION

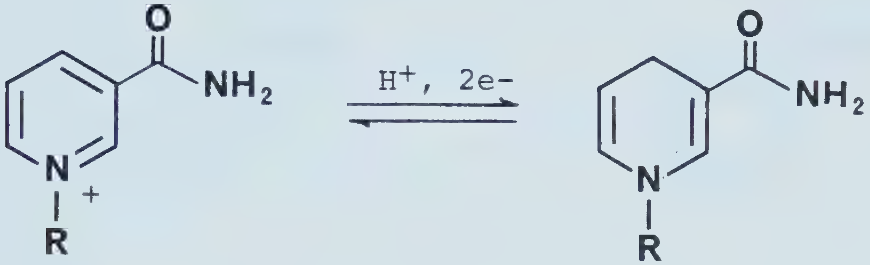
1.1.0.0.0 Pharmacology of dihydropyridines.

In 1851 Thomas Anderson discovered and isolated pyridine from deer horns[1]. The chemical formula of pyridine was subsequently established by Ladenburg in 1888[1]. The structural similarity between benzene and pyridine has stimulated an ever increasing interest into studies of pyridine chemistry.

A number of pyridine compounds have assumed important roles in biochemistry and pharmacology. The Vitamin B_6 complex is composed of pyridoxones which serve as co-factors in the enzymatic catalysis of a variety of biochemical reactions[2]. Nicotine is an important constituent of tobacco, which acts as a depressant at autonomic ganglia[3].

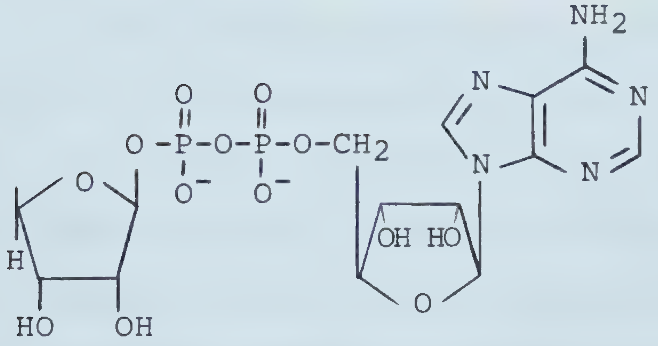
The discovery in the 1930's that nicotinamide adenine dinucleotide (NAD^+-NADH)(I) was a "hydrogen-transferring coenzyme" of importance to biological systems[4,5] has led to an increased interest in dihydropyridines for possible biochemical and pharmacological properties. These studies have resulted in the development of a variety of 1,4-dihydropyridines which exhibit antibacterial[6], antineoplastic[7,8], analgesic[9,10], hypotensive[11,12], spasmolytic[10,13,14], antiinflammatory[15] and porphyria inducing activities[16].

Wolfbeis and coworkers[17] recently manufactured red and violet dyes possessing conjugated 1,2- and 1,4-dihydropyridine ring systems as integral structural components of the chromophore.



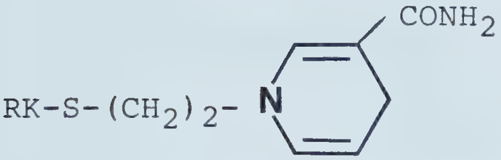
NAD I NADH

R=

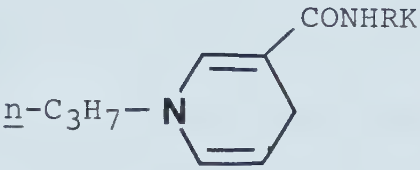


The importance of the NAD-NADH system to biological processes has stimulated investigation into a variety of model compounds which mimic the natural 1,4-dihydropyridine system[18-28]. Polymers have been utilized to covalently bind nicotinamide for use as a NADH model[27]. Two 1,4-

dihydropyridines (II and III) covalently bound to reduced keratin have also served as models for the functional study of the NAD-NADH system[28].



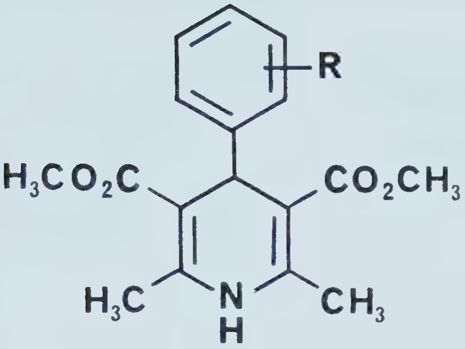
II



III

RK = reduced keratin

In 1882 Hantzsch developed a procedure for the synthesis of 1,4-dihydropyridines which now bears his name[29]. An excellent review describing this synthesis and the pharmacological properties of the Hanztsch 4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (IV) has recently been published[30]. Nifedipine (Adalat$^{(R)}$) (IV-a)[31-38] and SKF 24260 (IV-b)[39-44], developed independently by Pharma der Bayer and Smith, Kline and French respectively, are calcium channel antagonists. The coronary dilating and hypotensive properties of IV-a and IV-b have been used effectively to treat hypertension and reduce the frequency of attacks in angina pectoris[30]. In the last few years several potent antihypertensive



(a), R = o-NO_2

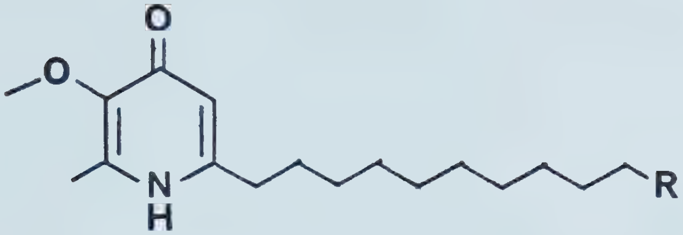
(b), R = o-CF_3

IV

drugs[45-49] have been developed via structural modification of the parent compound IV.

A number of 1,4-dihydropyridine alkaloids (V) have also been isolated from the plant *Melochia pyrimidata*[50-53]. These alkaloids are structurally similar to the Chinolon alkaloid VI isolated by Kapadia and coworkers from *Melochia tomentosa*[54].

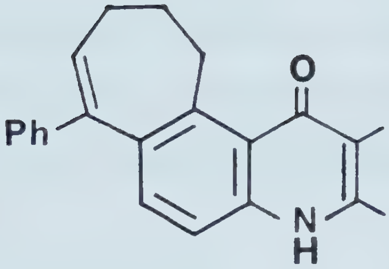
The literature describing other dihydropyridines is concerned primarily with the use of these compounds as intermediates in the synthesis and biosynthesis of pharmacologically important alkaloids. Buchi and coworkers[55] reported the first total synthesis of an iboga alkaloid by employing a reactive 1,6-dihydropyridine in a Diels-Alder cycloaddition reaction. Several other studies have employed 1,2- and 1,6-dihydropyridine derivatives to synthesize other



V

Melochinine R = $CH(OH)CH_3$

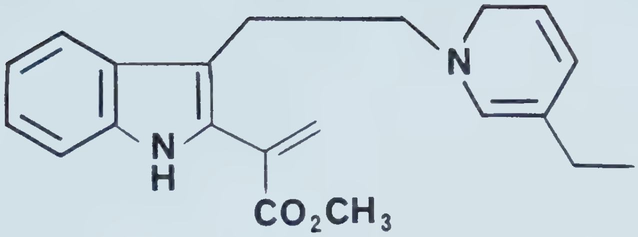
Melochininone R = $COCH_3$



VI

alkaloids of this class[56,57]. The iboga alkaloids have pharmacological properties similar to cocaine in that they potentiate the pressor action of adrenaline[58]. Dehydrosecodine B (VII), an unstable 1,6-dihydropyridine, has been proposed as a biosynthetic precursor to the iboga alkaloids[57,59].

Edwards and coworkers[60] have prepared penicillin compounds VIII having 2-and 4-pyridones as the heterocycle. Pyridones VIII-a and VIII-b display activity

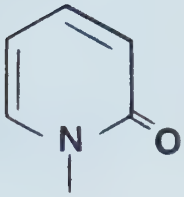


VII

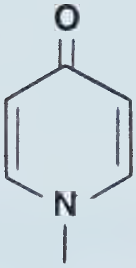
against gram positive and gram negative bacteria similar to those of ampicillin. Substitution of the pyridone ring (VIII-c, VIII-d) results in a decrease of antibacterial activity.

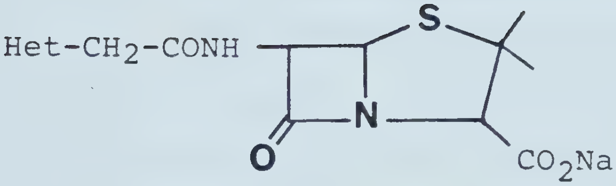
Dihydropyridines have also served as pro-drugs for the delivery of a quaternary pyridinium salt through a biological membrane. The preferred antidote for organophosphate poisoning is N-methylpyridinium-2-carbaldoxime chloride (2-PAM) (IX). The salt 2-PAM is not able to cross the blood-brain barrier in sufficient concentration to degrade the organophosphate[61]. Bodor and coworkers[62] have synthesized pro-2-PAM (X) which is a hydrochloride salt of the unstable 1,6-dihydropyridine XI.

(a), Het =



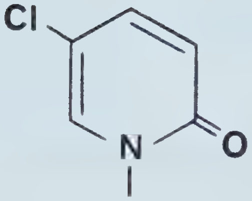
(b), Het =



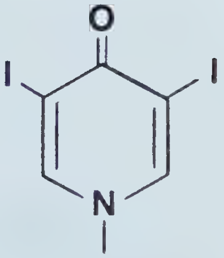


VIII

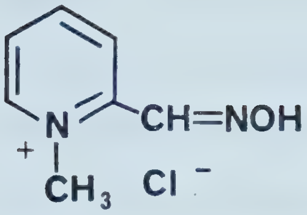
(c), Het =



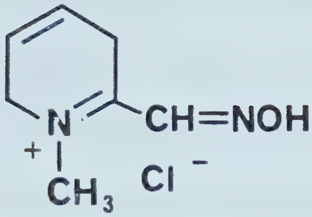
(d), Het =



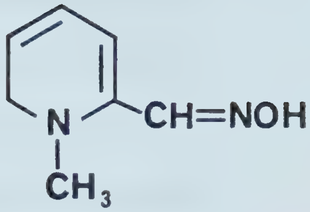
Pro-2-PAM enters the brain in high levels[63], following injection, where it is reconverted into 2-PAM.



IX



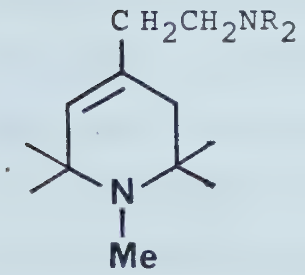
X



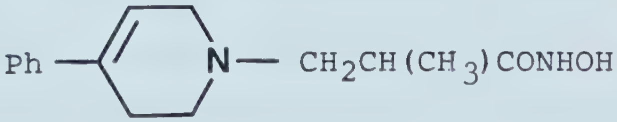
XI

1.2.0.0.0 Pharmacology of tetrahydropyridines.

The pharmacological literature of tetrahydropyridines is sparse. The greatest attention has focused on the 1,2,3,6-(or 1,2,5,6-) tetrahydropyridines, many of which are potent hypotensive agents. Amines XII are strong ganglionic blocking agents in various animals[64]. The propionohydroxamic acid XIII acts as a hypotensive by its ability to block α-adrenergic pathways[65].



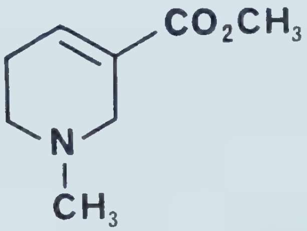
XII



XIII

The hypotensive properties of arecoline (XIV) are weak[66]. It has found use as an anthelmintic and cathartic in Echinococcus infections of the dog[67]. Knaus and coworkers[68-70] prepared a series of N-(carbonylamino)-1,2,3,6-tetrahydropyridines with analgesic, antiinflammatory and hyperglycemic properties.

A review on pyridines and reduced pyridines of pharmacological interest has been published[71].

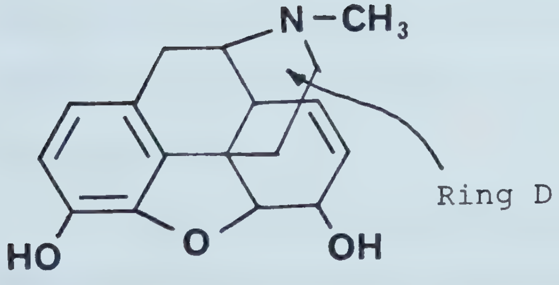


XIV

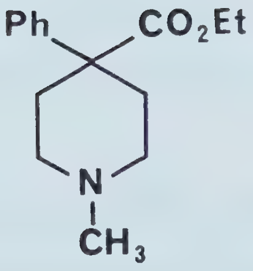
1.3.0.0.0 Pharmacology of piperidines.

In comparison to dihydropyridines and tetrahydropyridines, the pharmacological literature for piperidine compounds is immense. The piperidino moiety is often a replacement for a tertiary amino group, such as dimethylamino, in a drug molecule since their basic properties are similar. A more compact cyclic structure such as piperidine is often advantageous compared to diethylamino and higher alkylamino functions which possess free rotating alkyl groups.

The piperidine ring system is an important structural portion of many narcotic analgesics. The naturally occuring polycyclic alkaloid morphine (XV) features a fused piperidine ring (Ring D). A totally synthetic piperidine narcotic analgesic known as meperidine (XVI) was synthesized in 1939 by Eisleb and Schauman[72]. Meperidine has found wide usage for mild and moderate pain, especially in the relief of labor pain. The addictive liability and toxicity of XVI is lower than that observed with morphine[73].

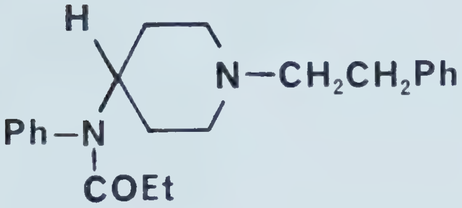


XV

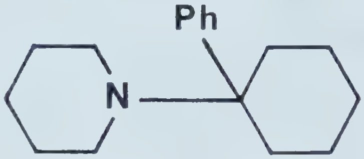


XVI

The good analgesia obtained with meperidine has stimulated further studies involving narcotic analgesics which possess a piperidine ring system. Fentanyl (XVII) and phencyclidine (XVIII) are two of the more potent and widely used derivatives. Fentanyl (XVII) is a high potency analgesic which is two hundred times more active as a pain killer in mice than morphine[74]. Fentanyl is used clinically as an analgesic[75] and as an adjunct in anaesthesiology[76]. Phencyclidine (XVIII) initially held promise as a safe general anaesthetic[77]. It is now a drug of abuse.

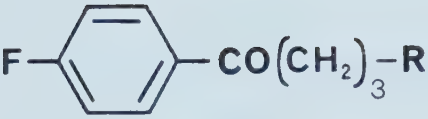


XVII



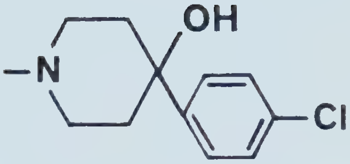
XVIII

The butyrophenones represent a potent and specific class of antipsychotics, of which haloperidol XIX-a and spiroperidol XIX-b are prototype members. Many of the butyrophenones exhibit pharmacological activity similar to chlorpromazine and related phenothiazines[78]. The most prominent side effects observed with butyrophenones and

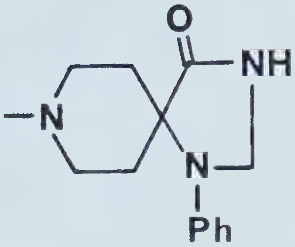


XIX

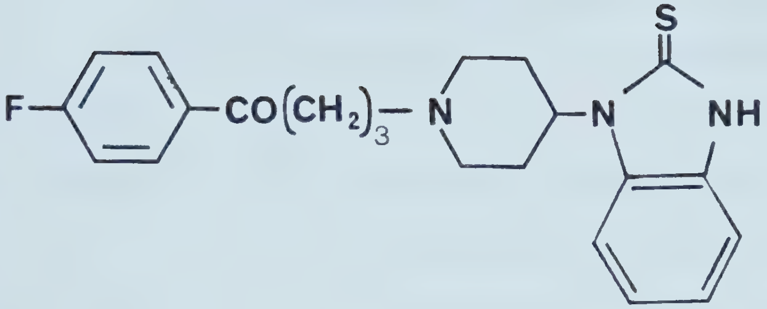
a; Haloperidol R =



b; Spiroperidol R =



neuroleptics in general are extrapyramidal in nature. Sato and coworkers[79] have recently reported a butyrophenone compound (XX) having a potency similar to haloperidol but with a low incidence of side effects.



XX

1.4.0.0.0 The chemistry of 1,4-dihydropyridines.

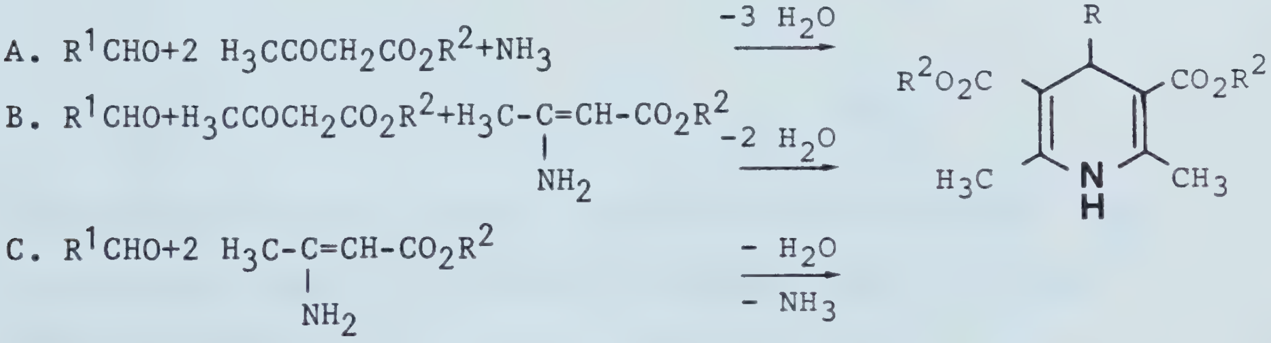
The use of model NAD-NADH systems and the development of hypotensive agents such as nifedipine and SKF 24260 have stimulated an increasing interest in the chemistry of 1,4-dihydropyridines[12]. The 1,4-dihydropyridines may also serve as potential pro-drugs. Eisner and Kuthan[12] and then Lyle[80] published reviews which surveyed recent developments describing the synthesis, structural elucidation and physical and chemical properties of 1,4-dihydropyridines. The chemistry of 1,4-dihydropyridines will be discussed in depth with particular emphasis on recent developments pertinent to this thesis.

1.4.1.0.0 Synthesis of 1,4-dihydropyridines.

1.4.1.1.0 Synthesis of 1,4-dihydropyridines by condensation and cycloaddition reactions.

A general procedure for the preparation of highly substituted 1,4-dihydropyridines is provided by the Hantzsch ring closure[29]. The procedure involves the condensation of an aldehyde and β-ketoester (acetoacetate) in a molar ratio of 1:2 with ammonia (Scheme I-A). Two improved synthetic variations for the synthesis of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates have been reported (Scheme I-B and I-C)[81,82].

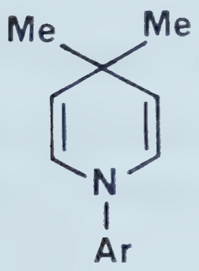
Scheme I: Synthesis of 2,3,4,5,6-pentasubstituted -1,4-dihydropyridines.


A. R¹CHO+2 H₃CCOCH₂CO₂R²+NH₃
-3 H₂O
B. R¹CHO+H₃CCOCH₂CO₂R²+H₃C-C=CH-CO₂R²
NH₂
-2 H₂O
C. R¹CHO+2 H₃C-C=CH-CO₂R²
NH₂
- H₂O
- NH₃
R
R²O₂C
CO₂R²
H₃C
CH₃
N
H

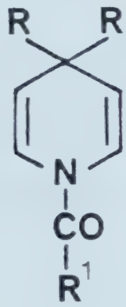
These procedures provide facile syntheses of calcium channel antagonists. Chennet and Eisner[83] employed methyl

propiolate as the β-ketoester derivative as outlined by Schemes I-A and I-B to synthesize 3,4,5-trisubstituted - 1,4-dihydropyridines.

Reactions of 3,3-dimethylglutaraldehyde with primary aryl amines afforded XXI in high yield[84]. The use of simple alkyl amines in place of aryl amines afforded the corresponding 1,4-dihydropyridines in low yields. Acid catalyzed condensation of carbamates or primary amides with glutaraldehydes produced XXII in high yield[85,86].



XXI



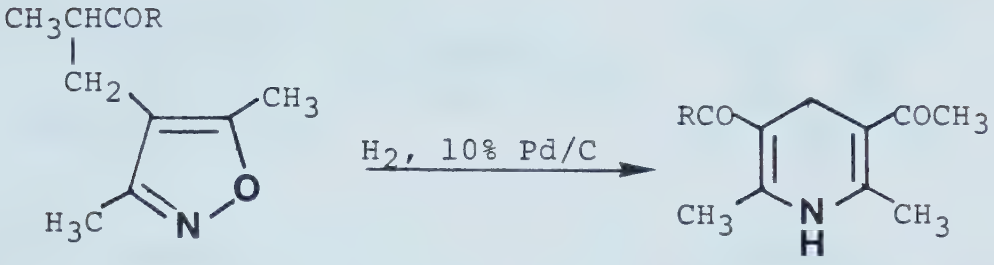
XXII

1,4-Dihydropyridines, having a hydrogen atom at the C-4 position, oxidize readily in air and therefore must be stored under nitrogen.

1.4.1.2.0 Synthesis of 1,4-dihydropyridines from other ring systems.

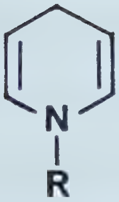
Catalytic hydrogenation of the isoxazole XXIII affords the 1,4-dihydropyridine XXIV[87,88]. The

reaction proceeds by hydrogenolysis of the N-O bond followed by recyclization and loss of water.

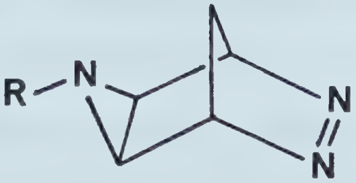


XXIII XXIV

The simple dihydropyridines XXV have been shown to arise via the spontaneous fragmentation of XXVI[89]. The loss of nitrogen to relieve ring strain in XXVI is the



XXV



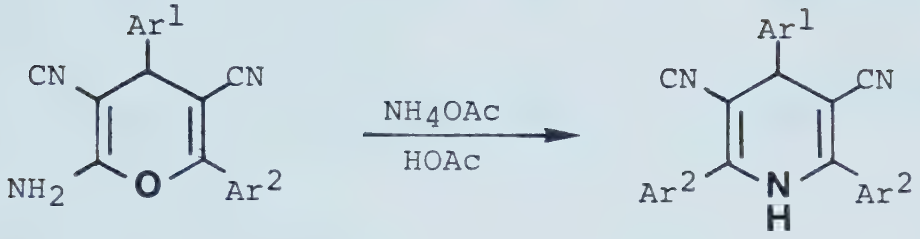
XXVI

R = CH_3, SO_2Ph, Ph, $(CH_2)_2Ph$

driving force behind the fragmentation.

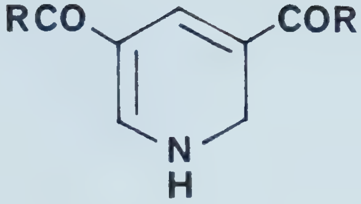
Treatment of the dihydropyran XXVII with ammonium acetate/acetic acid gives rise to the corresponding

1,4-dihydropyridine XXVIII[90].



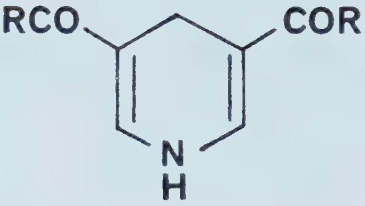
XXVII XXVIII

The isomerization of 1,2-dihydropyridines to 1,4-dihydropyridines has received little attention to date. Fowler[91] demonstrated that 1-methyl—1,2-dihydropyridine in the presence of strong base isomerized to the corresponding 1,4-dihydropyridine in 92% yield. Metal catalysts are also capable of isomerizing dihydropyridines. Thus, treatment of 1-trimethylsilyl- 1,2-dihydropyridine with palladium or rhodium catalysts affords the corresponding 1,4-isomer[92]. The 1,2-dihydropyridines XXIX undergo isomerization to the 1,4-isomers XXX in 70% yield using $RhCl(PPh)_3$. The corresponding aromatic pyridine is also formed in 30% yield[93].



XXIX

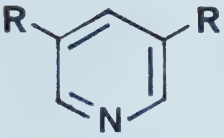
$R = CH_3, OCH_3$



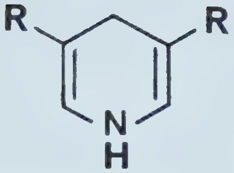
XXX

1.4.1.3.0 Synthesis of 1,4-dihydropyridines by nucleophilic addition of hydride using metal hydrides.

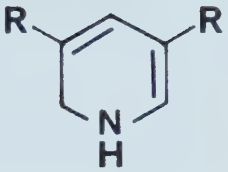
Reduction of pyridine and pyridinium salts with sodium borohydride affords 1,2-[94], 1,4-[95,96] and/or 1,6-dihydropyridines[97] as well as tetrahydropyridines[98,99]. In these reactions the product composition is influenced by the steric and electronic effects[100] exerted by the substituents and the nature of the solvent[101]. The choice of hydride reagent used also significantly influences the products obtained from the reduction of pyridines and pyridinium salts. For example, the reduction of diethyl pyridine-3,5-dicarboxylate (XXXI) using sodium cyanoborohydride yields the corresponding 1,4-isomer XXXII, whereas reduction using borane affords only XXXIII[101]. Reaction of 3,5-dicyanopyridine with sodium di(2-methoxy)ethoxydihydroaluminate (Redal, $NaAlH_2(OCH_2CH_2OCH_3)_2$) yields only the corresponding



XXXI



XXXII



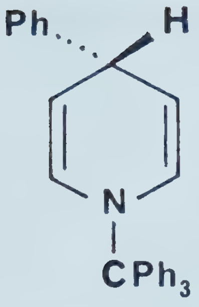
XXXIII

R = CO_2Et

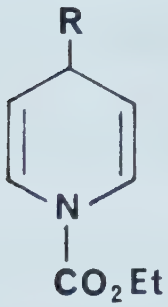
1,4-dihydropyridine[102]. These observations suggest the steric effect of the bulky hydride reagent plays an important role in determining the position of hydride attack.

1.4.1.4.0 Synthesis of 1,4-dihydropyridines using nucleophilic organometallic reagents.

Organometallic reagents attack preferentially at the C-2 or C-6[103] positions of pyridines and pyridinium salts; addition to the C-4 position is less common. Reaction of N-triphenylmethylpyridinium fluoroborate with phenylmagnesium bromide yields the 4-substituted - 1,4-dihydropyridine XXXIV[104]. The position of substitution is influenced by the steric effect of the N-triphenylmethyl moiety[105]. Treatment of 4-unsubstituted pyridines with ethylchloroformate and organocuprates at low temperatures gives rise to 1,4-dihydropyridines XXXV in high yield[106]. Akiba and coworkers[107] recently synthesized

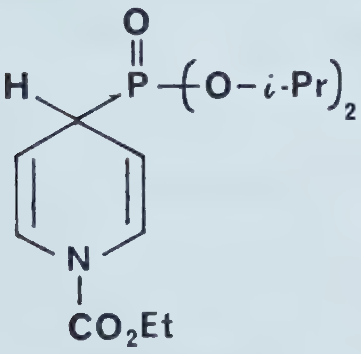


XXXIV

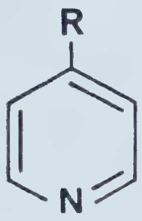


XXXV

XXXVI from the reaction of pyridine with ethyl chloroformate and triisopropyl phosphite. Alkylation of XXXVI at the C-4 position and rearomatization of the 1,4-dihydropyridine with butyllithium affords XXXVII. The



XXXVI



XXXVII

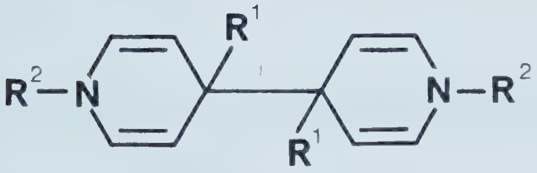
overall reaction described above is a regiospecific alkylation of pyridine at the C-4 position.

Preparation of XXXVII starting with pyridine has also been accomplished using ethylchloroformate and $RCu \cdot BF_3$.

In this case, the intermediate 1,4-dihydropyridine XXXV was converted to XXXVII under a stream of oxygen[108].

1.4.1.5.0 Miscellaneous syntheses of 1,4-dihydropyridines.

Reduction of pyridines and pyridinium salts with lithium metal and liquid ammonia in ethanol[109,110] yield simple 1-alkyl-1,4-dihydropyridines. The isolatable intermediate from this reaction is the dimeric dihydropyridine XXXVIII[109].

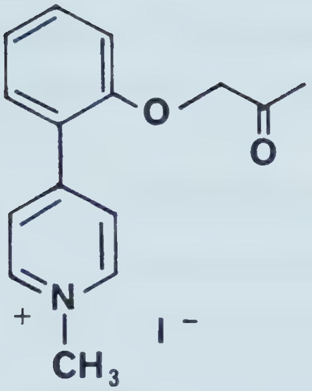


R^1 = H, CH_3
R^2 = H, CH_3, C_2H_5, $n\text{-}C_3H_7$, CO_2CH_3

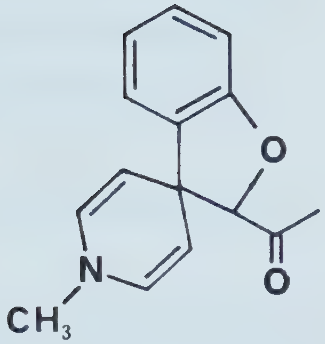
XXXVIII

Reduction of 3-substituted or 3,5-disubstituted pyridinium salts with sodium dithionite in mildly alkaline solution affords the corresponding 1,4-dihydropyridines[111-113] which have been employed as NAD-NADH model compounds[111-116].

Treatment of XXXIX with sodium hydroxide affords the 4-spiro-1,4-dihydropyridine XL in excellent yield[117].



XXXIX



XL

The addition of dilute acid to XL gives rise to XXXIX.

1.4.2.0.0 Physical properties of 1,4-dihydropyridines.

1.4.2.1.0 Ultraviolet absorption spectra of 1,4-dihydropyridines.

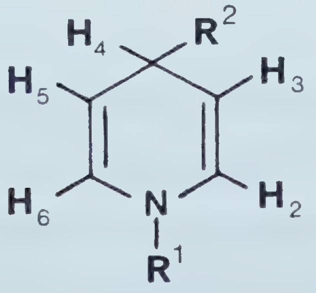
1,4-Dihydropyridines generally absorb light at shorter wavelengths (300 nm) than the corresponding 1,2-dihydropyridines which absorb at 350 nm. This effect is due to extended conjugation in the 1,2-dihydropyridine dienamine system. Substitution of electron-withdrawing substituents on nitrogen produces a hypsochromic shift[118,119].

1.4.2.2.0 Infrared spectra of 1,4-dihydropyridines.

The infrared spectra of 1,4-dihydropyridines are generally very simple. Characteristic stretching vibrations of medium to strong intensity in the 1500-1640 cm^{-1} region of the spectrum are due to the enamine system inherent in 1,4-dihydropyridines[119,120].

1.4.2.3.0 Proton magnetic resonance spectra of 1,4-dihydropyridines.

The proton chemical shifts for 1,4-dihydropyridines usually appear in the 4.2-6.2 δ range. The nature of the ring substitution pattern will influence the exact chemical shifts observed and the multiplicity of the resonances. The low to high field positions for the protons of symmetrical 1,4-disubstituted-1,4-dihydropyridines XLI are generally[94,110] H_2=H_6>H_3=H_5>H_4. Typical J values (Hz) are $J_{2,3}=8$, $J_{3,4}=3.5$, $J_{2,6}=2$ and $J_{3,5}=2.5$.



R^1 = alkyl, acyl, acyloxy

R^2 = alkyl, aryl

XLI

1.4.2.4.0 Mass spectra of 1,4-dihydropyridines.

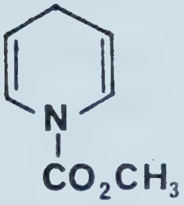
The most important fragmentation pattern in 4-substituted-1,4-dihydropyridines is the loss of the C-4 group as a radical to afford an aromatic pyridinium ion[121]. Further fragmentation is usually confined to the loss of fragments normally observed with pyridinium ions.

1.4.3.0.0 Chemical properties of 1,4-dihydropyridines.

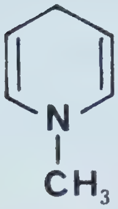
1.4.3.1.0 Stability and electronic structure of 1,4-dihydropyridines.

Highly substituted or polycyclic 1,4-dihydropyridines[122,123] are generally more stable than their counterparts having less functionality. Substitution of electron-withdrawing groups, capable of resonance interaction, at the 1-, 3- and/or 5-positions further enhances the stability of dihydropyridines. For example, N-carbomethoxy-1,4-dihydropyridine (XLII)[94] is more stable than N-methyl-1,4-dihydropyridine XLIII or 1,4-dihydropyridine XLIV.

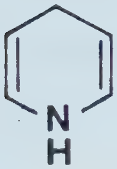
The low stability of 3-ethyl-1,2-dihydropyridine (XLV), an integral structural portion of dehydrosecodine B (VII), has been enhanced by complexation of the 1,6-dihydropyridine ring system with chromium carbonyl[124,125]. The labile 1,2-dihydropyridine (XLV)



XLII

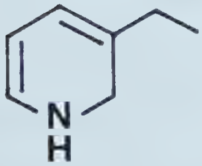


XLIII

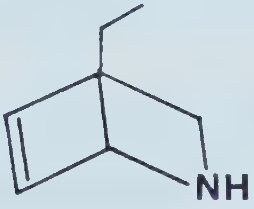


XLIV

has also been masked as a 2-azabicyclo[2.2.0]hex-5-ene bicycle (XLVI)[126]. The original dihydropyridine can be regenerated simply with mild heat.



XLV



XLVI

Molecular orbital calculations indicate that the nitrogen lone electron pair and the electrons of the two olefinic bonds for 1,4-dihydropyridines are not delocalized. Electron-withdrawing substituents at the C-3 and/or C-5 positions therefore enhance stability through substantial delocalization.

1.4.3.2.0 Oxidation of 1,4-dihydropyridines.

1,4-Dihydropyridines undergo oxidation by dehydrogenation[108] or disproportionation[127]. The hydrogen transfer capabilities of 1,4-dihydropyridines to pyridines[128] was fundamental to the elucidation of the mode of action of NADH.

1.4.3.3.0 Reduction of 1,4-dihydropyridines.

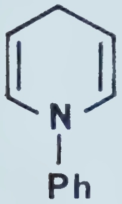
Reduction of 1,4-dihydropyridines using metal hydrides generally affords 1,2,3,4-tetrahydropyridines[96] while catalytic reduction with palladium on charcoal and hydrogen gas produces 1,2,3,4-tetrahydro- or hexahydro-pyridines[129].

1.4.3.4.0 Cycloaddition reactions of 1,4-dihydropyridines.

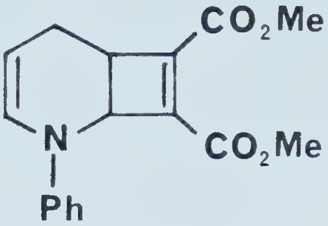
Diels-Alder adducts have been obtained from a variety of 1,2- and 1,6-dihydropyridines[130-132]. 1,4-Dihydropyridines do not undergo [4+2] cycloaddition reactions although they may serve as dienes for [2+1], [2+2] or [2+3] cycloaddition reactions. A review of cycloaddition reactions of pyridines and reduced pyridines has recently been published[133].

Reaction of XLVII with dimethylacetylenedicarboxylate (DMAD), in the absence of a proton donor, produces the unstable intermediate XLVIII which undergoes ring expansion

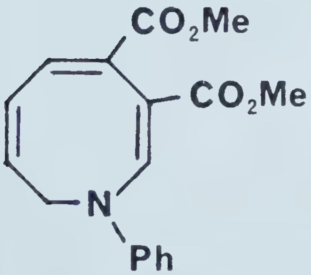
to afford the 1,2-dihydroazocine XLIX[134]. In the presence of a proton donor, XLVII and DMAD yields L[135].



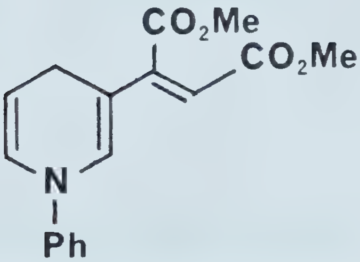
XLVII



XLVIII



XLIX

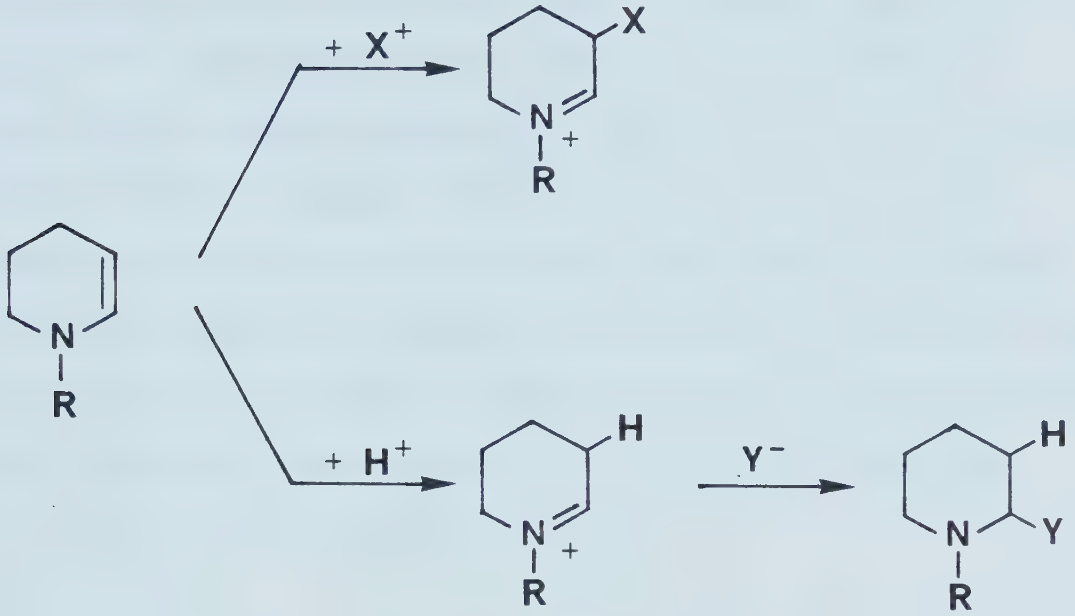


L

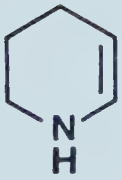
1.5.0.0.0 Chemistry of 1,2,3,4-tetrahydropyridines.

1,2,3,4-Tetrahydropyridines are cyclic enamines susceptible to attack by nucleophiles at C-6 and electrophiles at C-5 (Scheme II)[136].

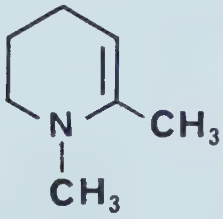
Scheme II: Reactions of nucleophiles and electrophiles with 1,2,3,4-tetrahydropyridines.



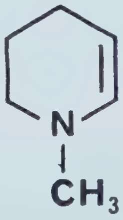
The presence of electron-withdrawing substituents at the 1-[137] and 5-[138] positions stabilizes the 1,2,3,4-tetrahydropyridines. The parent tetrahydropyridine LI has not been reported whereas simple N-substituted



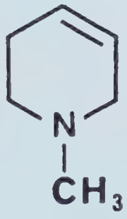
LI



LII

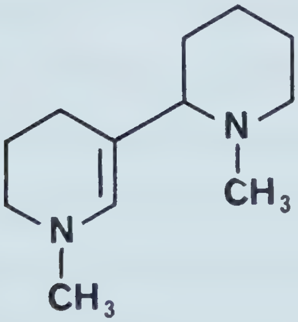


LIII



LIV

derivatives such as LII[139] and LIII[140] have been prepared. The preparation of LIII is achieved by isomerization of the corresponding 1-methyl-1,2,3,6-tetrahydropyridine LIV in strong base under anhydrous conditions[140]. Molecular orbital calculations indicate that LIII is thermodynamically more stable than LIV by 4.0 kcal/mole[140]. Strong π interaction of the nitrogen lone pair with the carbon-carbon double bond is possible for LIII. This interaction stabilizes the transition state involved in electrophilic substitution, thus promoting the acid catalyzed dimerization of LIII to N,N′-dimethyl-1,4,5,6-tetrahydroanabasine LV[141].



LV

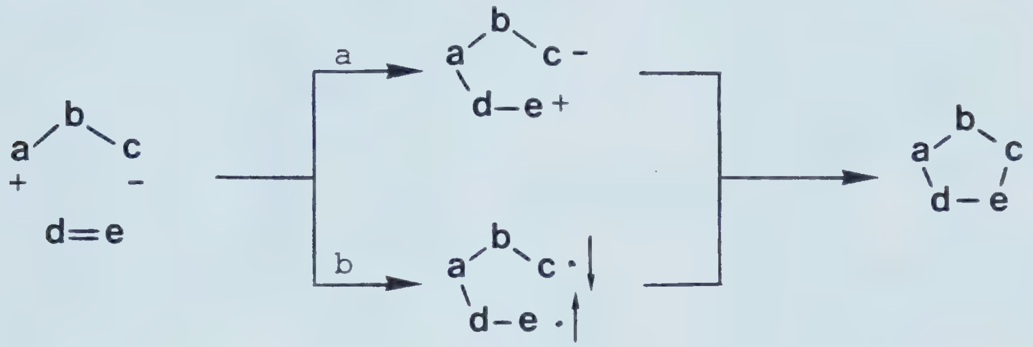
1.6.0.0.0 1,3-Dipolarcycloaddition reactions of enamines with organic azides.

The chemistry of 1,3-dipolarcycloaddition reactions has been reviewed in detail[142,143]. These reactions involve the concerted addition of a 1,3-dipole to a dipolarophile to produce five membered rings of varying stability. Common 1,3-dipoles include nitrile oxides, azides, ylides, carbonyl imines and diazoalkanes. The most common dipolarophile is the carbon-carbon double bond. The reactivity of the alkene may be increased by conjugation with nitrogen in an enamine system to afford an electron-rich dipolarophile. Electron-withdrawing groups such as the cyanosubstituent in cyanoethylenes, yield electron-deficient dipolarophiles which are also highly reactive.

Huisgen[142,144] proposed that the cycloaddition proceeds by a two-step process wherein the two new sigma (σ) bonds are formed separately via a dipolar species (Scheme III-a). An alternative two-step mechanism[145] incorporates a spin-paired diradical as the short lived intermediate (Scheme III-b). Both schemes account for the stereoselective "cis" addition observed in 1,3-dipolarcycloaddition reactions.

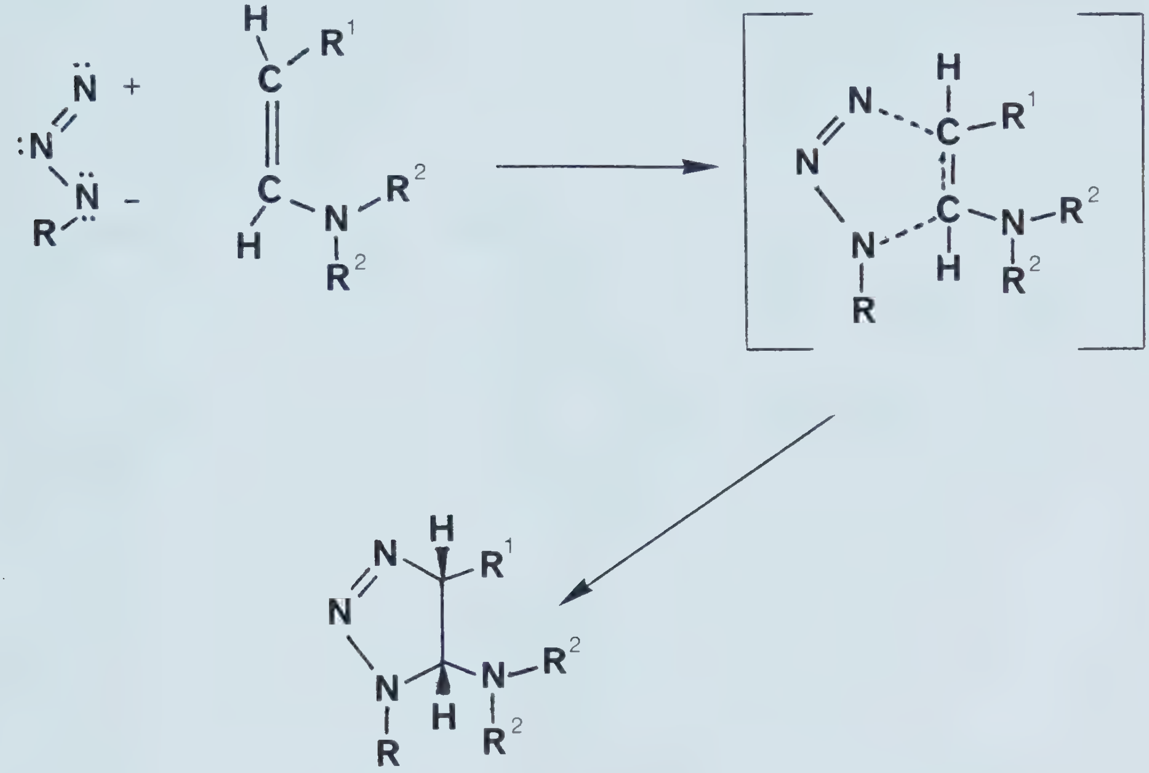
Addition of organic azides to enamines is generally under the control of electronic effects. The enamine

Scheme III: Possible mechanisms for 1,3-dipolar-cycloaddition of a dipolarophile and a dipole.

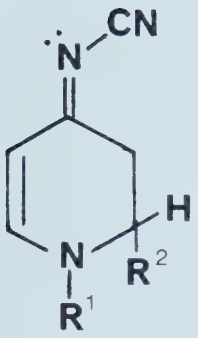


undergoes nucleophilic attack at the α-carbon by the azide nitrogen bearing the substituent and electrophilic attack at the β-carbon by the terminal azide nitrogen (Scheme IV). Azides containing electron-withdrawing substituents react more readily with electron-rich double bonds and vice versa[146]. This can be attributed to a partially charged transition state. When an electron-withdrawing group is attached to the nitrogen of the triazoline ring, the ring system is quite labile. Decomposition of the triazoline leads to aziridines, imines or a mixture of both[147].

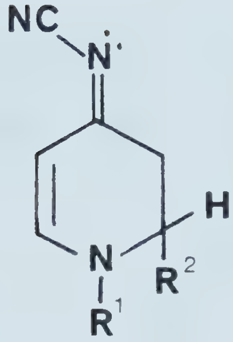
Scheme IV: 1,3-Dipolarcycloaddition of enamines to organic azides.



Ondrus and coworkers[148-150] investigated the reaction of organic azides with 1,2-dihydropyridines. Addition of cyanogen azide to N-substituted- 1,2-dihydropyridines affords a 1:1 mixture of E- and Z-1,2,3,4-tetrahydropiperidylidene-4-cyanamides LVI and LVII. The diazabicyclo[4.1.0]hept-4-enes LIX are obtained in quantitative yield from the reaction of 2-substituted-1,2-dihydro-



LVI

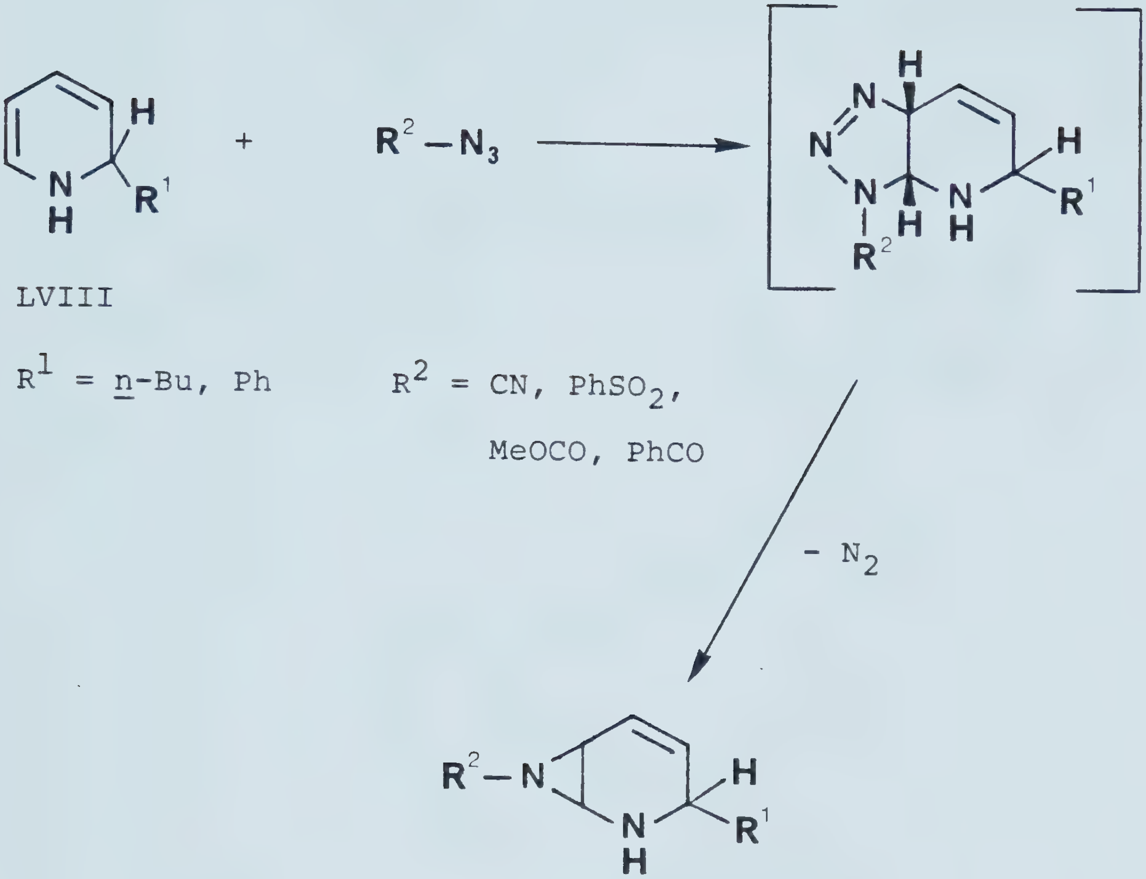


LVII

R^1 = CO_2Me, SO_2Me

R^2 = H,Ph, n-Bu

pyridines LVIII with organic azides[150]. The regiospecific cycloaddition of the azide to the 5,6 carbon-carbon double bond gives an unstable triazoline adduct which spontaneously loses nitrogen to provide LIX.



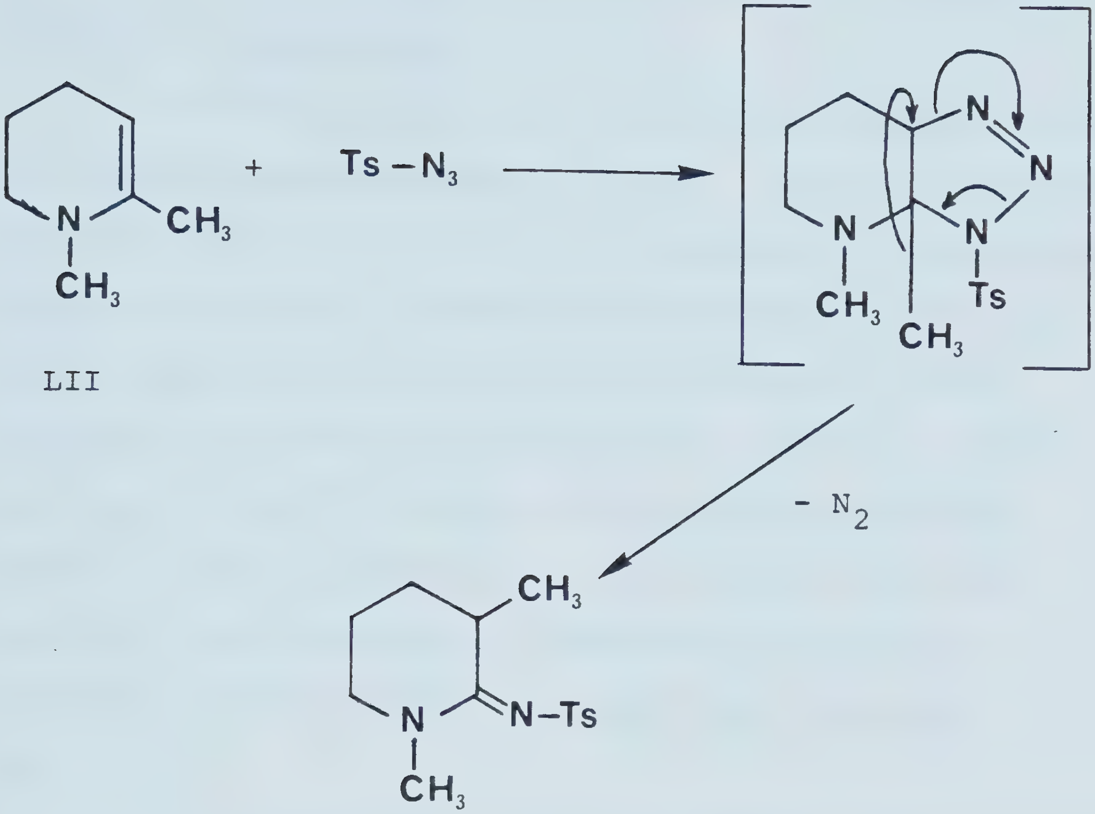
LVIII

R^1 = n-Bu, Ph

R^2 = CN, $PhSO_2$, MeOCO, PhCO

LIX

The addition of p-toluenesulfonyl azide ($Ts-N_3$) to 1,6-dimethyl-1,2,3,4-tetrahydropyridine (LII) affords 1,3-dimethylpiperidylidene-2-(4-methyl)benzenesulfonamide (LX)[151]. The formation of LX was postulated to arise by fragmentation of the triazoline with subsequent migration of the 6-methyl substituent.



LII

LX

1.7.0.0.0 Pharmacology of opiate and opioid analgesics.

1.7.1.0.0 Introduction.

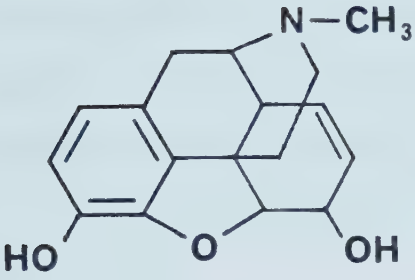
In 1799 Serturner first identified morphine as the principle narcotic component of opium. This discovery provided the impetus for further developments in the field of narcotic analgesics. Human experimentation in the mid-1800's established opium and morphine as very potent analgesics which had an unprecedented impact on medical practise. Kramer[152] recently published an excellent review on opiate analgesics in the 19th and early 20th centuries. He described the increasing importance of narcotics to the physician as agents for the relief of pain.

In this treatise, the term "opiates" will be used in reference to alkaloids and synthetic narcotic analgesics while the term "opioids" will refer to endogenous peptides.

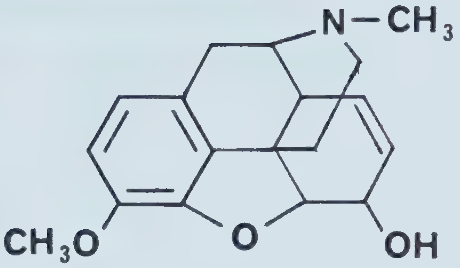
1.7.1.1.0 Natural opiates.

Morphine (XV) is the major alkaloid obtained from the poppy plant *Papaver somniferum* since it is present to the extent of 9% in the seed capsules[153]. The excellent pain-killing action of XV is accompanied by highly undesirable respiratory depression and physical dependence properties. Morphine and morphine-like compounds have been

implicated for use in a variety of ailments including intractable and postoperative pain.



XV



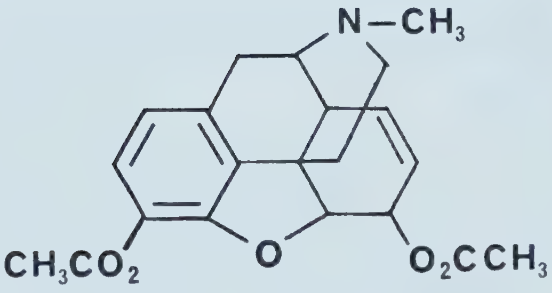
LXI

Codeine (LXI), a minor constituent of opium (0.3%), exhibits approximately one-seventh the analgesic potency of morphine and possesses a low physical dependence capability[153]. The reduced addiction potential of codeine served as a stimulus for synthetic modification of the morphine nucleus. Synthetic morphine analogues are being developed in an attempt to reduce dependence properties while maintaining analgetic activity.

1.7.1.2.0 Semi-synthetic and synthetic opiate analgesics.

The chemical transformation of morphine, codeine

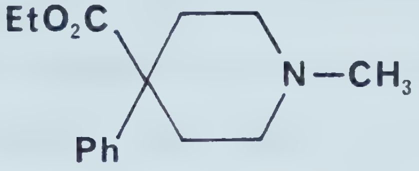
and other phenanthrene alkaloids produces analgesics referred to as semi-synthetic opiates. A greater analgesic potency than morphine has been realized with many of these compounds. Unfortunately, the side effects and dependence liabilities for a large number of semi-synthetic opiates are similar to or more pronounced than those of morphine[154,155]. Acetylation of morphine gives the potent and highly addictive analgesic diacetyl morphine, commonly called heroin (LXII).



LXII

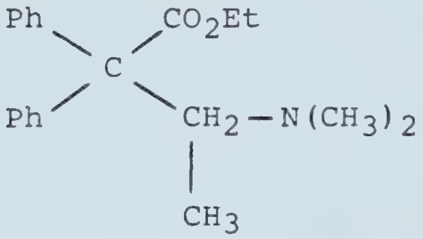
The total chemical synthesis of opiate analgesics was initiated with the hope that simpler homologues having chemical features similar to morphine could be developed which retained only the desirable analgetic properties. In 1939 Eisleb and Schaumann[72] prepared meperidine (XVI),

an analgesic which has since been accepted as a substitute for morphine. Meperidine was the first useful narcotic analgesic not derived from the phenanthrene alkaloid nucleus.



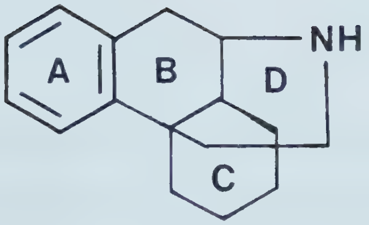
XVI

Methadone LXIII is an open chain analogue of meperidine having pharmacological properties comparable to morphine. Methadone is used clinically as a substitute for morphine in withdrawal treatment and in long term heroin and morphine rehabilitation therapy[156]. The pharmacological activity of methadone as well as most natural and synthetic opiates resides in the levo isomer.

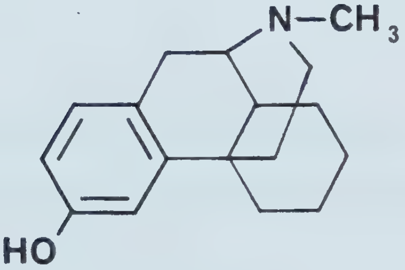


LXIII

A simplification of the morphine nucleus by removal of the ether linkage provides the morphinan group (LXIV). Levorphanol (LXV) is a typical representative of the morphinan analgesics which possess good analgesic qualities[157]. Unfortunately, levorphanol exhibits marked dependence liability and respiratory depressant characteristics[158].

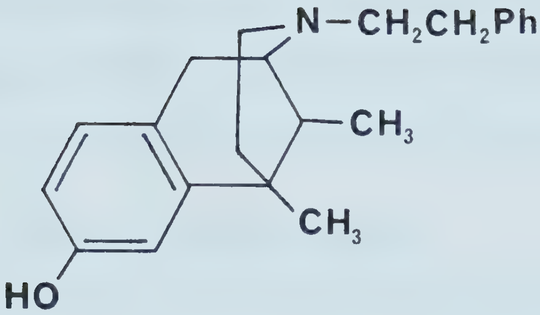


LXIV



LXV

The 6,7-benzomorphans which arise from simplification of the C ring in morphinans (LXIV) still possess narcotic analgesic action. Phenazocine (LXVI) exhibits three to five times the activity of morphine in man, and appears to have somewhat lower addiction potential than morphine[159]. Replacement of the N-CH_3 substituent of morphine (XV), levorphanol (LXV) and similar



LXVI

analgesics by an N-phenylethyl group, as demonstrated by phenazocine, generally confers a three to ten fold increase in analgesic activity.

These opiate analgesics possess a number of structural features critically linked to their powerful actions on the central nervous system. The four essential features which have been unequivocally identified are[160]:

(a) a flat aromatic structure which is usually a phenyl ring

(b) a central carbon atom attached to the aromatic moiety

(c) a tertiary amino group, one functionality generally being methyl

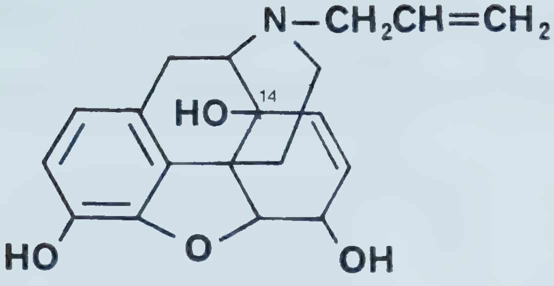
(d) a two carbon chain separating the central carbon

atom from the tertiary amino group.

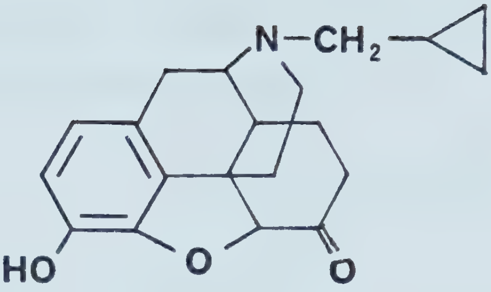
Significant structural deviation from any of these four points invariably leads to a significant reduction or complete loss of analgetic potency. The following section will demonstrate that minor structural modifications of the functionalities on the tertiary amino group result in major pharmacological changes in analgesic properties.

1.7.1.3.0 Narcotic Antagonists.

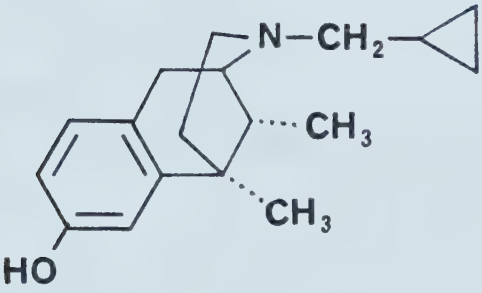
Replacement of the N-methyl group with larger N-alkyl substituents generally provides either pure narcotic antagonists or partial agonist-antagonists. Narcotic antagonists, although structurally similar to opiate agonists, have substantially different pharmacological properties. Naloxone (LXVII) is a prototype antagonist which inhibits all pharmacological effects of morphine including analgesia, respiratory depression and physical dependence[161]. In addition, LXVII is devoid of analgesic and dependence properties. Naloxone is useful in clinical practice[162] for morphine overdose treatment or narcotic addiction screening. Naltrexone (LXVIII) and cyclazocine (LXIX) are also extensively used as antagonists[163]. Incorporation of a hydroxyl group at the C-14 position of morphine alkaloids and 6,7-benzomorphans enhances their antagonist properties[164]. The hydroxyl



LXVII



LXVIII



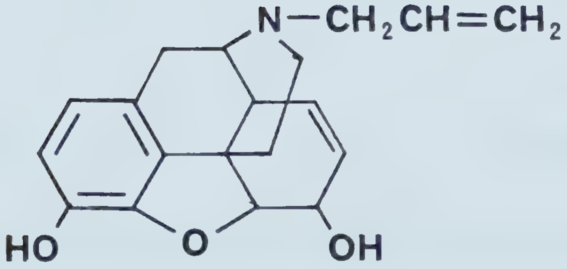
LXIX

group is thought to increase the rigidity of the ring system allowing for improved binding of the antagonist to the narcotic receptor site.

1.7.1.4.0 Partial agonist-antagonists.

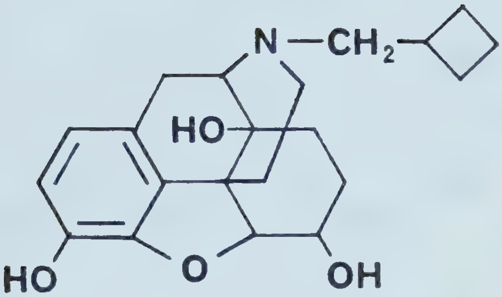
Nalorphine (LXX), the N-allyl derivative of morphine, was the first opiate found to demonstrate antagonist properties[165]. Low doses of nalorphine

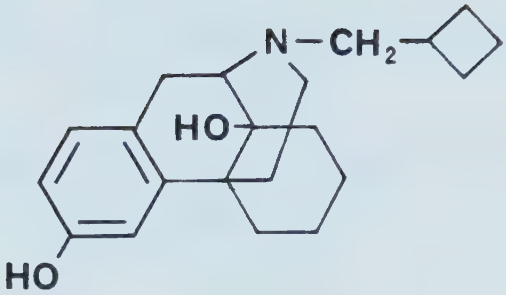
primarily elicit an analgesic response while antagonist properties are apparent at higher doses. Nalorphine is therefore a classical partial agonist. Chronic administration of LXX produces a mild physical dependence combined with relatively painless withdrawal[166]. The desirable properties of good analgesia and low physical dependence potential of nalorphine fueled the development of similar partial agonists with improved analgesia-dependence properties.



LXX

Two new partial agonists recently marketed in Canada are nalbuphine (Nubane^{R}) (LXXI)[167] and butorphanol (Stadol^{R}) LXXII[168,169]. The analgesic potencies of LXXI and LXXII are comparable to morphine while their physical dependence liabilities are "essentially negligible".

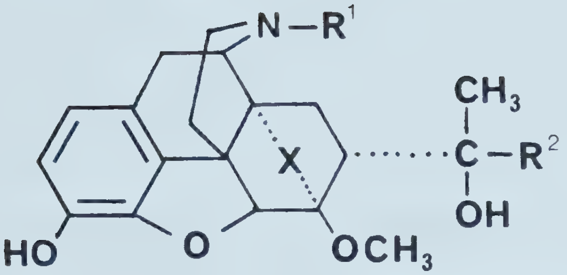




LXXI

LXXII

The general structure LXXIII represents an interesting class of oripavine alkaloid derivatives. Etorphine LXXIII-a) is a true narcotic agonist[170] whereas diprenorphine (LXXIII-b) is an almost pure narcotic antagonist[171]. A very potent partial agonist devoid of addictive properties is represented by buprenorphine (LXXIII-c)[172,173].



(a), $R^1 = CH_3$, R^2 = n-Pr,
X = -CH=CH-

(b), $R^1 = CH_2$-c-C_3H_5, $R^2 = CH_3$,
X = $-CH_2CH_2-$

(c), $R^1 = CH_2$-c-C_3H_5, R^2 = t-Bu
X = $-CH_2CH_2-$

LXXIII

1.7.1.5.0 Endogenous opioid peptides.

The excellent analgesia elicited by small doses of narcotic opiates suggests the existence of highly specific opiate receptors. The innate occurence of the receptors[174] further implies the existence of corresponding endogenous substances in the brain capable of initiating an analgesic response to a pain-producing stimuli. In 1975 Hughes and coworkers[175] identified two brain peptides, known as methionine(met)-enkephalin (LXXIV) and leucine-(leu)-enkephalin LXXV, which demonstrated analgesic properties. The amino acid sequence tyrosine(tyr), glycine (gly), glycine (gly) and phenylalanine(phe) are common to both pentapeptides. It is postulated that a specific enkephalin

tyr-gly-gly-phe-met
LXXIV

tyr-gly-gly-phe-leu
LXXV

conformation is required to "fit" the opiate receptor[176,177]. The rigid morphine molecule is thought to assume a similar conformation capable of mimicking the natural receptor response.

Tyrosine, the first amino acid in the enkephalin peptides, is likely the major structural group involved in enkephalin-receptor binding. The flat aromatic ring of tyrosine probably binds to a receptor area similar to that of the phenyl ring of morphine[178]. The other amino acids in the enkephalin peptides are probably involved in secondary binding to the opioid receptor.

Met- and leu-enkephalins may be derived from larger polypeptides. The amino acid sequence of β-lipotropin, a ninety-one amino acid peptide, is identical in the 61-65 region to that of met-enkephalin. In addition, β-endorphin, a thirty-one amino acid peptide formed in the cleavage of β-lipotropin, also has met-enkephalin as its first five amino acid sequence[175]. The amino acid sequence of leu-enkephalin corresponds to the first five residues found in

the seventeen amino acid peptide dynorphin[179,180]. β-Endorphin[181,182] and dynorphin[180], like the enkephalins, elicit analgesic responses.

The endogenous opioid peptides are almost certainly involved in nociception control[183]. Many other physiological functions have been credited to the opioid peptides including roles in obesity[184], Parkinsonism[185], hypertension[186], neurotransmission[187,188] and hormonal level control[189].

1.7.2.0.0 Opiate and opioid receptors.

1.7.2.1.0 General considerations.

Opiate and opioid receptors which are confined to nervous tissue have been identified only in vertebrate species[190]. At this time compelling evidence favors the existence of distinct morphine and enkephalin receptors. A number of different classification systems have been used to delineate the multiple analgesic receptors. The resulting nomenclature is complex; terminology such as mu (μ), kappa (κ), sigma (σ), delta (δ), episilon (ε), type I, type II, high affinity, low affinity, O_1 and O_2 have been used to describe various receptor types. Detailed reviews concerning analgesic receptors have been published[191-193]. The following discussion will focus on the identification of receptors, pharmacology of typical receptor compounds and

physiological-pharmacological factors affecting binding of opiates and endogenous opioids to receptors.

1.7.2.2.0 Narcotic opiate receptors. The μ, κ and σ receptor theory.

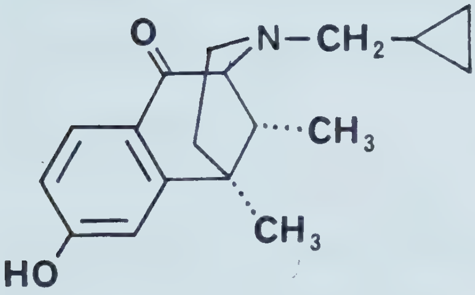
Three groups of investigators[194-196] independently demonstrated high affinity binding of opiates to rat brain tissue using tritium-labelled opiates. Treatment of [^{3}H]naloxone-bound brain tissue with various narcotic analgesics resulted in the displacement of tritiated naloxone from the opiate binding sites[194]. Using a chronic spinal dog model, Martin and coworkers postulated the existence of three distinct narcotic opiate receptors termed mu (μ), kappa(κ) and sigma(σ). The properties of these receptors, which form the basis for all opiate receptor theories, may be summarized as follows:

(a) μ-receptor. Morphine (XV) and etorphine (LXXIII-a) are prototype agonists of the μ-receptor. The binding of these compounds results in a general depression of nociceptive responses, miosis, bradycardia and hypothermia.

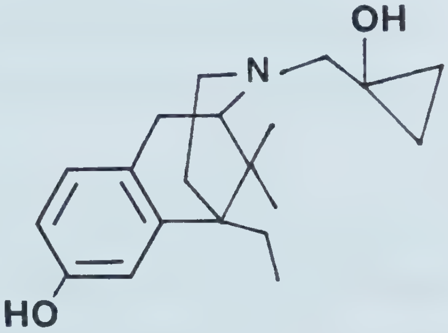
(b) κ-receptor. Ketocyclazocine (LXXVI) and bremazocine (LXXVII)[197] are the prototype agonists of the κ-receptor. The interaction of these compounds at the κ-receptor site causes sedation as well as depression of both the nociceptive response and the flexor

reflex. The pupils become constricted whereas the pulse rate and skin twitch reflex remain unaltered.

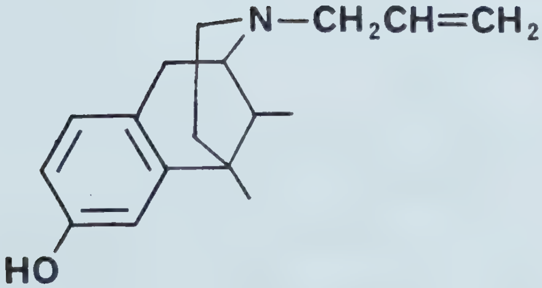
(c) σ-receptor. N-allylnormetazocine (SKF 10,047) (LXXVIII) is the prototype agonist of the σ-receptor. A typical response is characterized by mydriasis, tachypnea, tachycardia and mania. Apomorphine (LXXIX) and SKF 10,047 exhibit similar pharmacological activity.



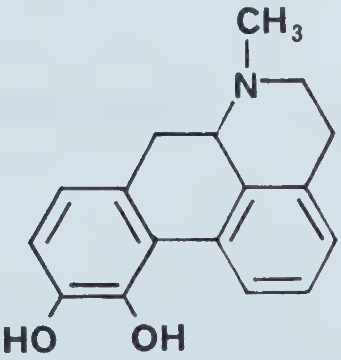
LXXVI



LXXVII



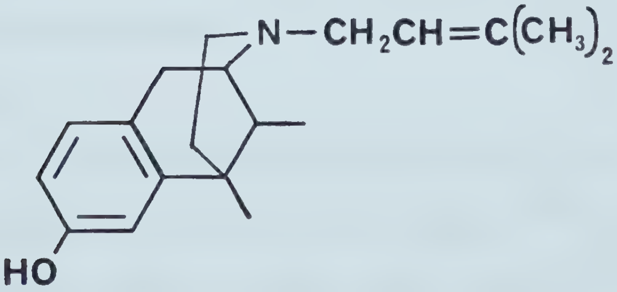
LXXVIII



LXXIX

All receptor subtypes are inhibited by narcotic antagonists such as naloxone and naltrexone. The antagonist dose required to block κ-effects is 20-60 times that required to effect a μ-blockade[198]. In the morphine-dependent dog ketocyclazocine does not suppress a withdrawal reaction. The reverse is also true, morphine treatment of a ketocyclazocine dependent dog does not suppress withdrawal[199]. Specific agonists tend to induce tolerance in their respective receptors and drug dosages must be continually augmented in order to obtain a consistent level of response.

In the μ, κ and σ-receptor system partial agonists usually exert their effect by antagonizing a particular receptor while exerting their agonist properties on another receptor class. The typical partial agonists nalorphine



LXXX

(LXX), butorphanol (LXXII) and pentazocine (LXXX) act as antagonists at the μ-receptor and as agonists at the κ-receptor[198-200].

1.7.2.3.0 Endogenous opioid receptor.

The endogenous opioids do not conform to the μ, κ and σ-receptor system model. Enkephalins have a low affinity for the μ-receptor and an even lower affinity for the κ-receptor[201,202]. All of the opiate receptors interact poorly with β-endorphin[203].

Although an opioid peptide neuronal system postulate was formulated as early as 1975[204], the existence of specific endogenous opioid receptors was not proposed until 1977[205]. Lord and coworkers[205] proposed a high affinity-high efficacy binding site called the delta (δ) receptor with which the enkephalins and β-endorphin both interact. Many modifications and elaborations of the original δ-receptor model have been made since its conception but the fundamental principles of the theory are still accepted today.

Several other theories describing additional receptor systems have been advanced. Schulz[206] demonstrated the presence of a specific epsilon receptor (ε) responsive only to β-endorphin. A selective receptor has been postulated[207] and identified[208] for the seventeen-amino acid peptide dynorphin. The receptor has not been named,

however, it is pharmacologically similar to the κ-opiate binding site.

1.7.2.4.0 Conformational changes in the opiate receptor.

A number of cofactors have been identified which induce conformational changes in the opiate receptor and thus affect opiate binding. Sodium ions (Na^+), and to a lesser extent lithium ions (Li^+), enhance the binding of antagonists such as naloxone to the μ-receptor while inhibiting the binding of the corresponding agonists[209]. The effect of Na^+ on the κ-receptor binding is less pronounced than that observed at the μ-receptor[210-212]. The sodium ion also decreases the affinity of enkephalin for the δ-binding site[213]. Sodium ions enhance the binding of partial agonists at the μ-receptor, the site of their antagonistic activities. In contrast, Na^+ slightly inhibits binding at the κ-receptor where the partial agonists elicit their analgesic effects[211,214].

A select number of divalent cations reverse the effects of monovalent cations on receptor binding. Magnesium (Mg^{+2}), nickel (Ni^{+2}) and in particular manganese (Mn^{+2}) counteract the ability of sodium ions to inhibit agonist binding[215]. In addition, the divalent cations by themselves enhance μ-opiate agonist affinity. Receptor binding of the opioid peptides β-endorphin

and met-enkephalin, in contrast to that of opiate μ-agonists, is inhibited in the presence of Mg^{+2} and Mn^{+2} [216].

The opiate receptors are very sensitive to inactivation by protein modifying reagents such as iodoacetamide and N-ethylmaleimide which react with free sulfhydryl groups[195,217]. Proteolytic enzymes such as trypsin, chymotrypsin and phospholipase A also effectively destroy receptor function[218,219]. It is interesting to note that pretreatment of opiate receptors with Na^+ protects them from protein modifying reagents[220,221]. A conformational change in the receptor site induced by Na^+ protects receptor sulfhydryl groups from inactivation. Investigative evidence further indicates that this conformational change is identical to the one responsible for enhanced antagonist and reduced agonist binding[191]. These observations suggest that protein moieties form an intrinsic part of the opiate receptor binding mechanism. At the present time there is no data available regarding the effects of protein modifying reagents and proteolytic enzymes on opioid receptor systems.

1.7.2.5.0 Recent opiate and opioid receptor models.

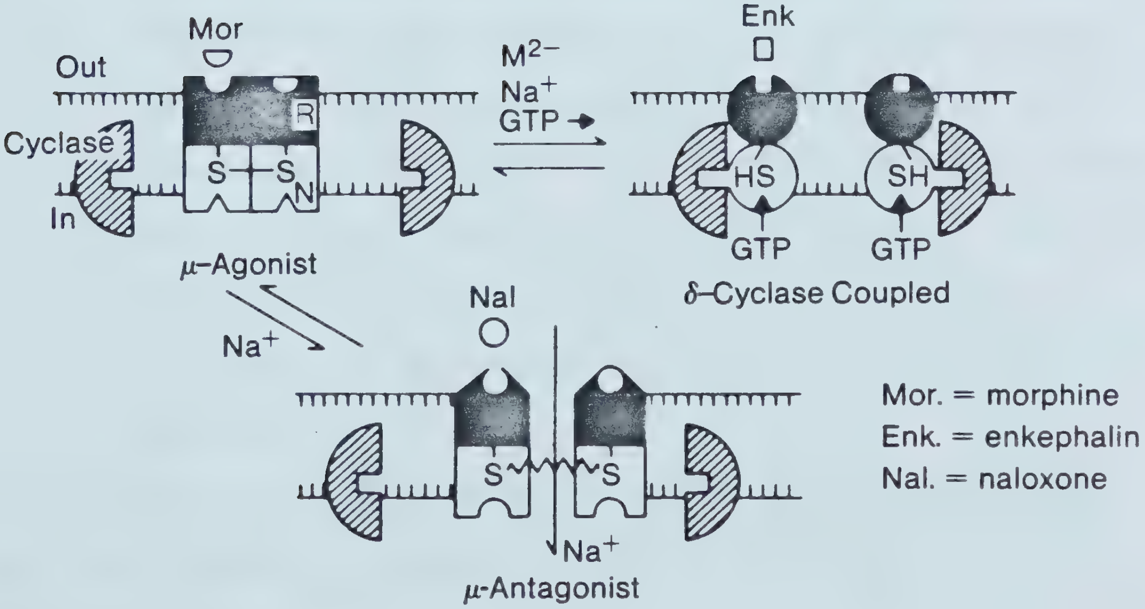
The physiological effects of sodium ions, divalent cations and protein modifying reagents and the discovery of new opiates and endogenous opioid peptides has spawned a

variety of new receptor models. Many investigators[189,192,222] continue to relate opiate and opioid analgesic effects to the five receptor system (μ, κ, σ, δ and ε). Chang and coworkers[223] grouped opiate and enkephalin receptors into seven classifications according to the relative binding potency and the effects of sodium ions on receptor activity. The existence of a κ-receptor has been questioned by Hiller and Simon[224]. Their studies using the rat central nervous system indicate that tritium-labelled ethylketocyclazocine, a typical κ-agonist, has a CNS binding distribution pattern simlar to μ-agonists. Kosterlitz and coworkers[225] however recently characterized theκreceptor subtype as accounting for approximately 30% of the opiate receptor. These diametrically opposed reports arise as a result of variation in the interpretation of pharmacological data using a multiple-receptor model.

In spite of their complexity, multiple receptor theories still fail to provide an unmitigated explanation of observed biochemical responses. In recent years several simple receptor hypotheses have been advanced. Buatti and Pasternak[226] proposed a model consisting solely of "high" and "low" affinity receptors which mediate analgesic action and respiratory depressant effects, respectively. Opiate and opioid binding sites have also been discussed in terms of one heterogeneous receptor in combination with the μ and δ-receptor sites[227,228]. The κ, σ and ε-binding

sites were considered merely modifications of the primary μ and κ-receptors.

An interesting three state allosteric opiate receptor has recently been proposed[229,230]. The receptor accommodates a μ-agonist, μ-antagonist and an adenylate cyclase-coupled δ-agonist state. The equilibrium among the three possible states is mediated by Na^+, guanosine triphosphate (GTP) and the configuration of the receptor sulfhydryl groups. The μ-agonist-antagonist receptor (also



referred to as Type I receptor) is characterized by highly discrete brain localization, receptor sulfide bonding and inhibition by GTP. Introduction of Na^+ enhances μ-antagonist binding at the direct expense of μ-agonist binding. Adenylate cyclase/coupled δ-binding (Type II receptor) is promoted by GTP and slightly by Na^+. The type II receptors are specific for enkephalins and are diffusely distributed in the brain. The model fails to explain the binding of partial agonist opiates or endogenous peptides such as β-endorphin and dynorphin.

In summary, opiate-opioid receptors can perhaps best be described as follows[227]:

> "It is possible to conceive different opiates binding to the same receptor, even to the same receptor in different ways, so that subsequent disposition of the receptor becomes variable. Thus multiple receptors, receptor overlap, different receptor conformations or some combination of these possibilities cure are all potential explanations of the data just discussed."

A completely satisfactory model system which accommodates all known narcotic receptor information has yet to be developed.

1.7.2.6.0 Receptor morphology.

Despite the abundance of opiate-opioid receptor theories, little information concerning the gross and

detailed morphological features of narcotic receptors is available. The effects of protein modifying-reagents[195,217] and proteolytic enzymes[218,219] on receptor function discussed earlier indicate that an integral part of the receptor structure is protein.

Lee and Smith[231] suggested a narcotic receptor composed of protein and lipid with the enkephalins binding to protein, opiate alkaloids to lipid and β-endorphin to both. This proposal seems unlikely as protein modifying-reagents are known to affect opiate binding[195,217]. Macromolecular complexes which are partially composed of protein have been identified which bind etorphine[232,233] and enkephalin[234]. A recent study[235] described an opiate receptor comprised of a larger and smaller structural entity in which the smaller receptor was considered a subunit of the larger.

1.7.3.0.0 Structurally novel narcotic analgesics.

Narcotic receptor biochemical and physiological data accumulated during recent years has increased man's understanding of the mechanisms and control of pain. In addition, the recent cascade of information concerning narcotic analgesics and endogenous opioids has accelerated the search for more potent analgesics having fewer undesirable side effects. The information in the following discussion will focus on the development of narcotic analgesics during the

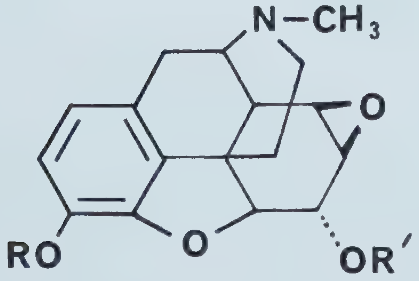
period 1977 to 1982.

1.7.3.1.0 Analgesics based on the alkaloid nucleus.

The excellent analgesia and relatively low addiction potential displayed by partial agonists such as buprenorphine (LXXIII-c) encouraged research into the preparation of high efficacy-low addiction pain killers. Many structural modifications of the morphine nucleus, morphinan and 6,7-benzomorphan structures have been devised in order to investigate their analgesic properties.

1.7.3.1.1 Alterations of the morphine nucleus.

Epoxidation of the olefinic bond of morphine (XV), codeine (LXI) and heroin (LXII) gives the corresponding 7,8-oxide (LXXXI)[236]. The analgesic potency of compounds LXXXI is approximately twice that of the corresponding parent compounds.



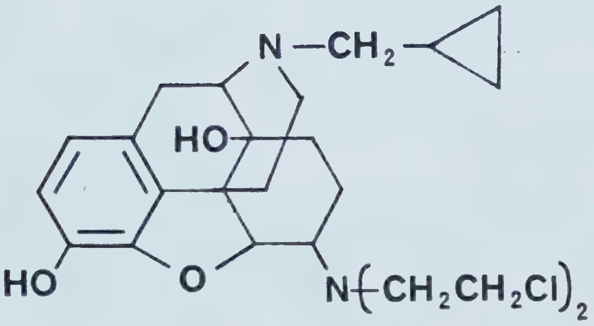
(a), $R=R'=H$ (morphine analogue)

(b), $R=CH_3$, $R'=H$ (codeine analogue)

(c), $R=R'=COCH_3$ (heroin analogue)

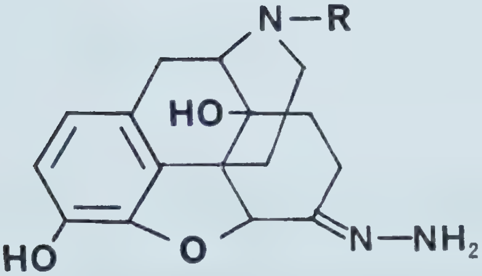
LXXXI

Portoghese and coworkers[237,238] synthesized the long-acting narcotic antagonist chlornaltrexamine (LXXXII). The reactive bis-(chloroethyl)amino group undergoes an alkylation reaction with the opiate receptor. A single dose of chlornaltrexamine therefore may have antagonistic activity for as long as three days.



LXXXII

Pasternak and coworkers[239,240] investigated another long-acting narcotic antagonist. Naloxazone (LXXXIII-a) is a hydrazine derivative of naloxone which binds covalently to the opiate receptor and remains active for periods of up to three days. The hydrazine derivates of oxymorphone[234,240], oxymorphazone (LXXXIII-b) exhibit long-acting agonist properties.



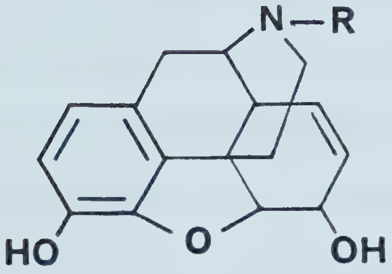
(a), R = $-CH_2CH{=}CH_2$

(b), R = $-CH_3$

LXXXIII

The N-sec-alkyl and N-tert-alkyl normorphines (LXXXIV) prepared by alkylation of normorphine exhibit interesting analgesic properties[241]. The tert-alkyl derivatives LXXXIV a-c are devoid of both agonist and antagonist activity while the sec-alkyl compounds LXXXIX d-e are partial agonists. The (S)-isomer of LXXXIV-d displays analgesic activity similar to morphine and antagonist

effects comparable to nalorphine.



(a), R = $C(CH_3)_2CH_2CH_3$

(b), R = $C(CH_3)_2CH=CH_2$

(c), R = $C(CH_3)_2CH_2Ph$

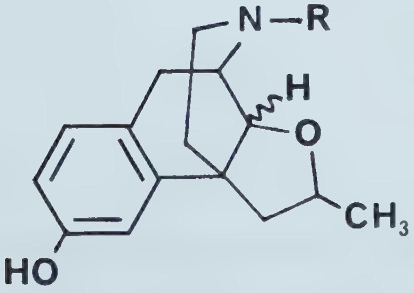
(d), R = $CH(CH_3)CH_2CH_3$

(e), R = $CH(CH_2CH_3)_2$

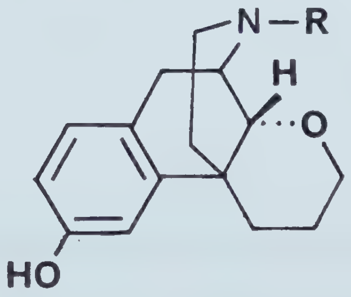
LXXXIV

1.7.3.1.2 Alteration of morphinan and 6,7-benzomorphans.

The synthesis and analgesic properties of tetrahydrofuranobenzomorphans(LXXXV) and 8-oxamorphans (LXXXVI)



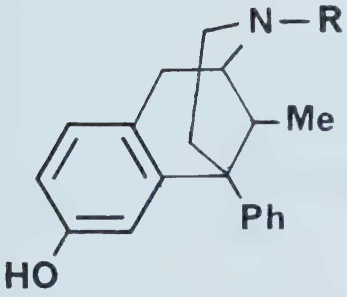
LXXXV



LXXXVI

have been described[242,243]. The analgesic activity of LXXXV is one-third that of LXXXVI when the R group for both is methyl. Incorporation of larger alkyl or cycloalkyl R substituents provides partial agonists with good activity.

The 5-phenyl-6,7-benzomorphan (LXXXVII) derivatives[244-246] act as narcotic opiates. The N-methyl analogue (LXXXVII-a) is a partial agonist possessing two to five times the analgesic potency of morphine. The N-phenylethyl compound LXXXVII-d is a weaker analgesic than the N-methyl derivative and shows no antagonistic action. Partial agonist activity is demonstrated by LXXXVII-b and c[245] while the N-propargyl compound LXXXVII-e is a pure narcotic antagonist[246].



LXXXVII

(a), $R=CH_3$

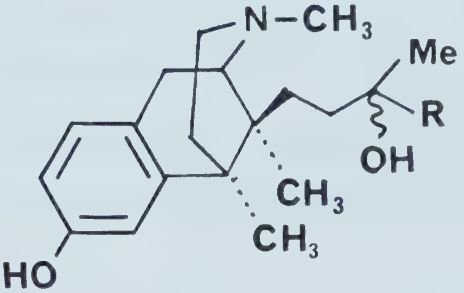
(b), $R=CH_2CH=C(CH_3)_2$

(c), $R=CH_2$-c-C_4H_7

(d), $R=CH_2CH_2Ph$

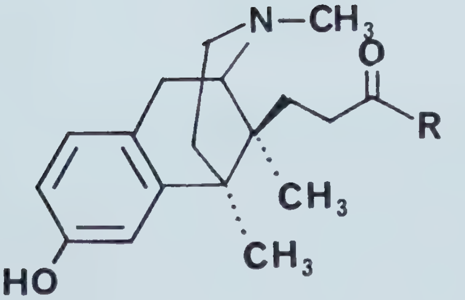
(e), $R=CH_2-C\equiv CH$

A novel series of 6,7-benzomorphans possessing structural features similar to the narcotic opiates etorphine, diprenorphine and buprenorphine (LXXIII) has been synthesized[247-249]. Compounds LXXXVIII are devoid of any analgesic agonist activity but exhibit three to five times the antagonist activity of nalorphine[248,249]. Compounds containing an N-methyl substituent generally act as agonists. Therefore, LXXXVIII represents a rare example of a N-methyl substituted pure narcotic antagonist. The corresponding alkanones LXXXIX exhibit a wide spectrum of narcotic analgesic activities[249]. Compounds containing



R = $\underline{t}$-Bu or $(CH_2)_2CH(CH_3)_2$

LXXXVIII



(a), R = $\underline{n}$-C_3H_7

(b), R = $\underline{n}$-C_4H_9

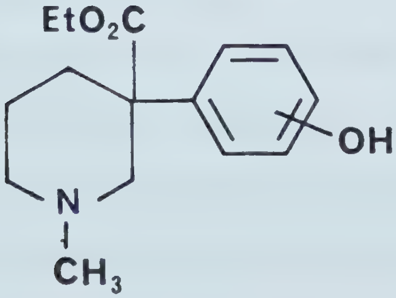
(c), R = $\underline{n}$-C_5H_{11}

LXXXIX

n-propyl (LXXXIX-a) or *n*-butyl (LXXXIX-b) R substituents are twenty to thirty times more potent than morphine and possess little or no antagonistic activity. The *n*-pentyl derivative LXXXIX-c is a partial agonist with analgesic activity three times that of morphine.

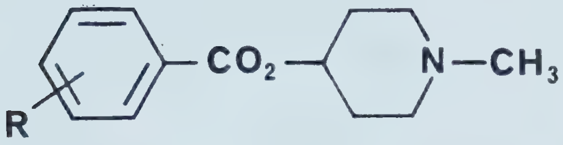
1.7.3.2.0 Structural modifications not based on a morphine nucleus.

A variety of structurally novel narcotic analgesics have been developed featuring a basic amino center and an aromatic nucleus. Piperidine compounds represent a particularly important class of analgesics of this type. The 3,3-disubstituted piperidines XC are analgesics based on the structure of meperidine[250,251]. The *m*-hydroxy phenyl isomer is the most potent derivative with an activity one-tenth that of morphine and equivalent to meperidine.



XC

Cheng and coworkers[252] investigated the quantitative structure-activity relationships of aromatic esters of 1-methyl-4-piperidonol (XCI). The 3,4-dimethoxyphenyl derivative is the most potent compound showing analgesic activity comparable to morphine. Cheng concluded that XCI required the following structural features in order to obtain maximal analgesic activity:



XCI

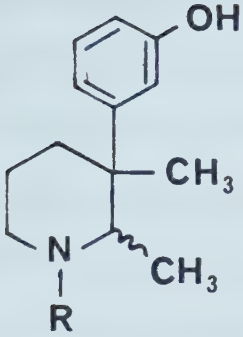
(a) the absence of ortho-phenyl substitution.

(b) meta- and para-substituents with good hydrogen-bonding acceptability and minimal width to minimize steric hindrance

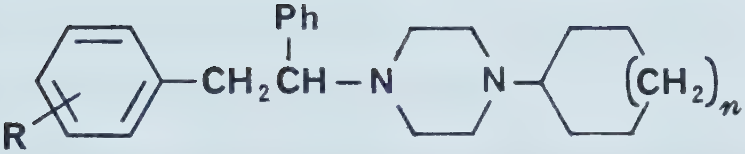
(c) N-substituents no larger than a methyl group.

Nalorphine-like properties are evident for the 2,3-dimethyl-3-arylpiperidines XCII[253]. The N-allyl and N-cyclopropylmethyl derivatives behave as pure narcotic antagonists.

N,N-Disubstituted piperazines XCIII are potent analgesics[254-256]. When R is 3-hydroxy[254], XCIII is an analgesic 25-55 times more active than morphine



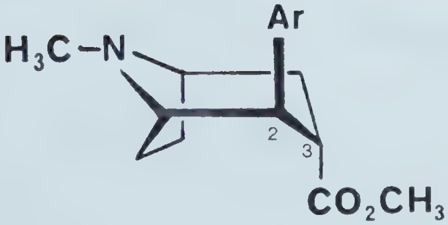
XCII



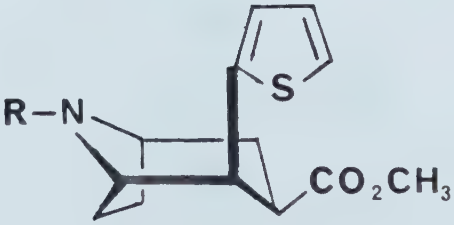
XCIII n = 1, 2 or 3

sulfate. Incorporation of a 4-OH or 4-H R substituent provides analgesics equipotent with morphine sulfate[255,256].

Clarke and coworkers[257,258] prepared tropane-3-carboxylic esters XCIV which exhibit narcotic analgesic



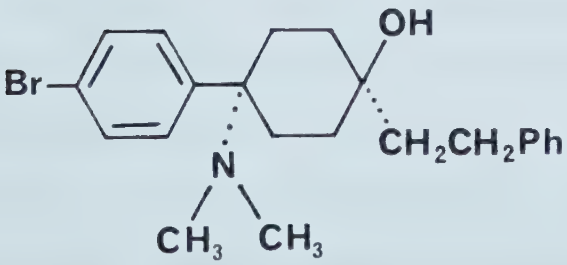
XCIV



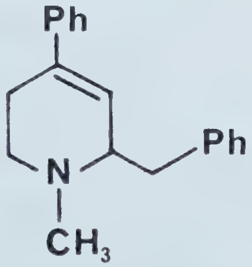
XCV R = H, CH_3, n-C_5H_{11}

activities. Those compounds, having an exo-aromatic group on C-2 and an endo-carbomethoxy group at C-3, are narcotic antagonists devoid of analgesic action[257]. Narcotic antagonist activity is not generally exhibited in opiates bearing an N-methyl substituent. The exo-2-thienyl-exo-3-carbomethoxy tropanes XCV are narcotic agonists having twice the activity of codeine[258]. A 60-80% reduction in blood glucose levels is also effected by XCV. Nalorphine antagonizes the analgesic properties of XCV but does not influence the hypoglycemic action.

A recent report describes an extremely potent opiate analgesic containing a basic nitrogen atom attached directly to a central carbon atom[259]. The trans-amino cyclohexanol XCVI is 10^4 times more potent than morphine sulfate. The agonist activity is blocked by naloxone.



XCVI



XCVII

1-methyl-2-benzyl-4-phenyl-1,2,5,6-tetrahydropyridine (XCVII) possesses analgesic activity similar to codeine yet is free of physical dependence liabilities[246].

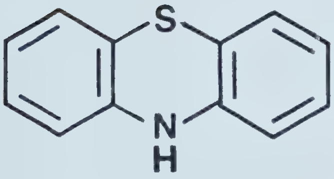
1.8.0.0.0 Testing for antinociception in opiates.

A variety of antinociception tests have been devised for analgesic compounds and several are commonly used with narcotic opiate analgesics. μ-Agonists are effective analgesics in heat (mouse hot plate and rat tail flick) and non-heat (mouse writhing and rat paw-inflamed) tests[260]. κ-Agonists are less effective in nociception heat tests although analgesic responses can be demonstrated using non-heat methods. σ-Agonists are inactive in both tests[261].

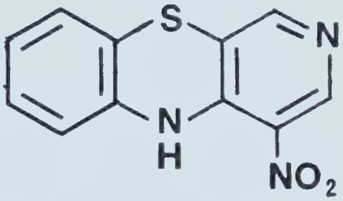
The phenylquinone and/or acetic acid writhing tests are especially useful for opiates. In general, potency as measured by writhing tests is directly proportional to clinical potency[262]. These tests are also accurate indicators of narcotic antagonist[261] and partial agonist activities[262]. Caution must be used in the interpretation of results from the phenylquinone writhing test in order to avoid false positives[263]. For example, physostigmine, pilocarpine and phenoxybenzamine which are atypical analgesics demonstrate analgesia in low doses in this test.

1.9.0.0.0 The chemistry of azaphenothiazines.

Phenothiazine (XCVIII) was accidentally discovered in 1883 during Bernthsen's structural studies of thiazine dyes[264]. This discovery led to the development of 10-dialkylaminoalkyl phenothiazines with medicinal properties such as tranquilizing, antihistaminic and antiemetic activities. In 1945 Petrow and Rewald[265] synthesized 1-nitro-3-azaphenothiazine (IC), the first heterocyclic analogue of a phenothiazine. In a detailed review describing the chemistry and pharmacology of azaphenothiazines, Okafor[266] outlined the many advances made in the 1-azaphenothiazine system. The following discussion will focus on some general aspects of azaphenothiazines and will emphasize recent developments in the largely unstudied 3-azaphenothiazine group.



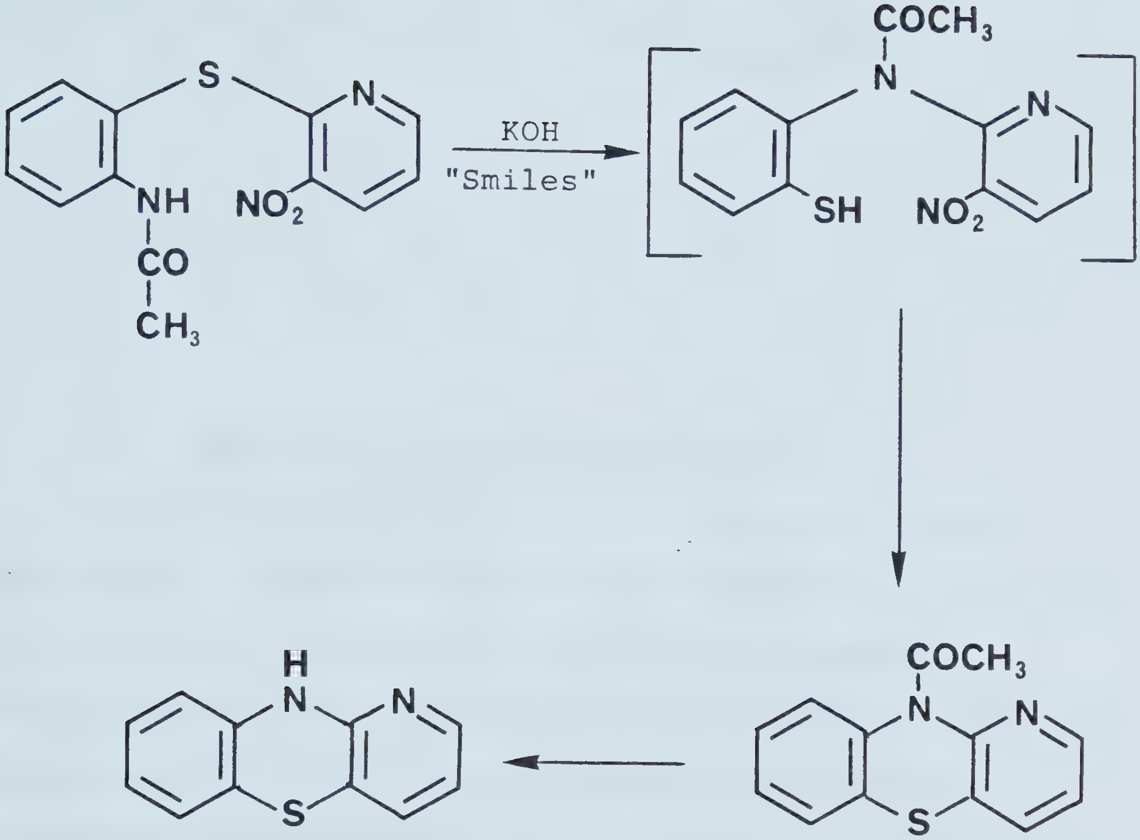
XCVIII



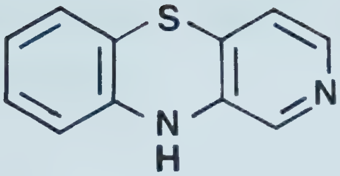
IC

1.9.1.0.0 Synthesis of the azaphenothiazine nucleus.

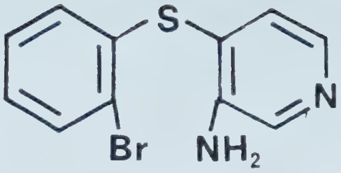
The Smiles rearrangement and subsequent ring closure is the most successful procedure for the preparation of azaphenothiazines reported to date. The Smiles rearrangement can be described as a nucleophilic aromatic substitution and involves the migration of an aromatic ring from one heteroatom to another. The majority of azaphenothiazines are synthesized by these reactions[266]. Yale and Sowinski[267] prepared 1-azaphenothiazine using the Smiles rearrangement reaction followed by cyclization of the heterocyclic sulfide with potassium hydroxide in acetone and 95% ethanol.



The most successful synthesis of 2-azaphenothiazine (C) reported to date is achieved by direct cyclization of CI using cuprous iodide and anhydrous sodium carbonate at 180-190°[268].



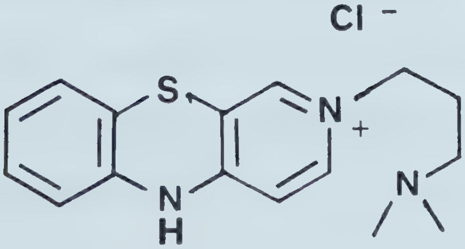
C



CI

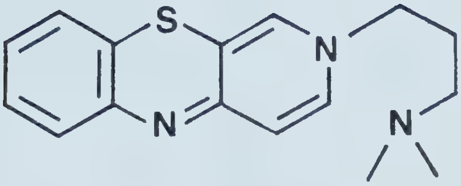
1.9.2.0.0 Reactions of azaphenothiazines.

Aminoalkylation of the N-10 nitrogen is readily accomplished. A common procedure involves heating the N-10 azaphenothiazine anion and an excess of an aminoalkyl chloride at reflux in a high boiling solvent for an extended period of time[267,269,270]. Alkylation of 3-azaphenothiazine with 3-dimethylaminopropyl chloride in the absence of strong base affords 3-(3-dimethylaminopropyl)-3-



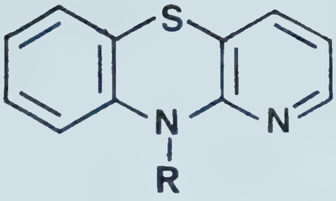
CII

azaphenothiazinium chloride (CII)[270]. Treatment of CII with aqueous alkali yields the corresponding anhydronium base CIII.

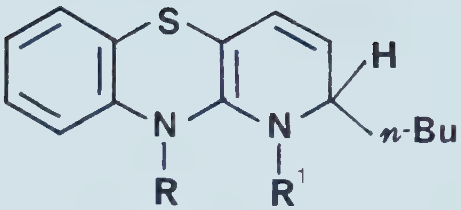


CIII

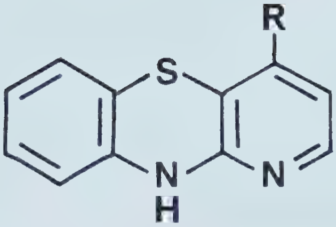
Reactions of 10-substituted-1-azaphenothiazines CIV with n-butyllithium and an electrophile such as methylchloroformate or diethylchlorophosphate generally afford the 1,2-dihydropyridine CV and a small amount of 4-substituted-azaphenothiazine CVI[271,272]. The reactivity of the electrophile influences the product distribution in this reaction. For example, treatment of CIV with n-butyllithium and the less reactive trifluoromethanesulfonyl chloride yields CVII and CVIII in a 1:3 ratio[272].



CIV



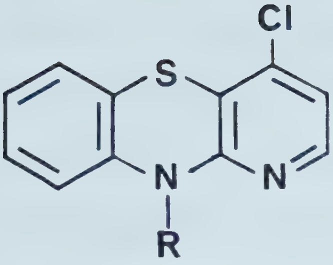
CV



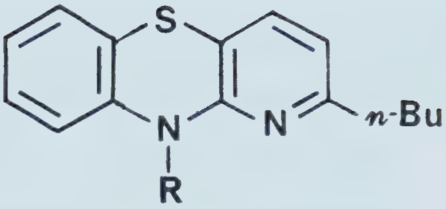
CVI

R=$-CH_3$, $-(CH_2)_3N(CH_3)_2$, R^1=$-CO_2CH_3$, $-(O)P(OE^t)_2$

$-CH_2CH(CH_3)N(CH_3)_2$



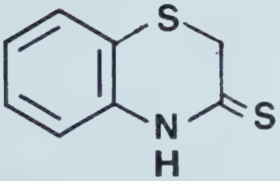
CVII



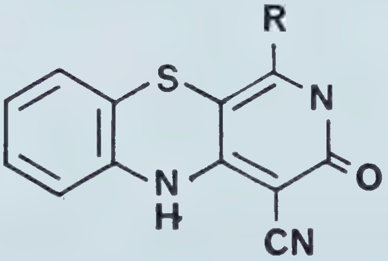
CVIII

R=as above for CIV

Literature concerning 3-azaphenothiazines in the last decade is sparse. A single communication on the synthesis of CX from the benzothiazine CIX has been described[273].



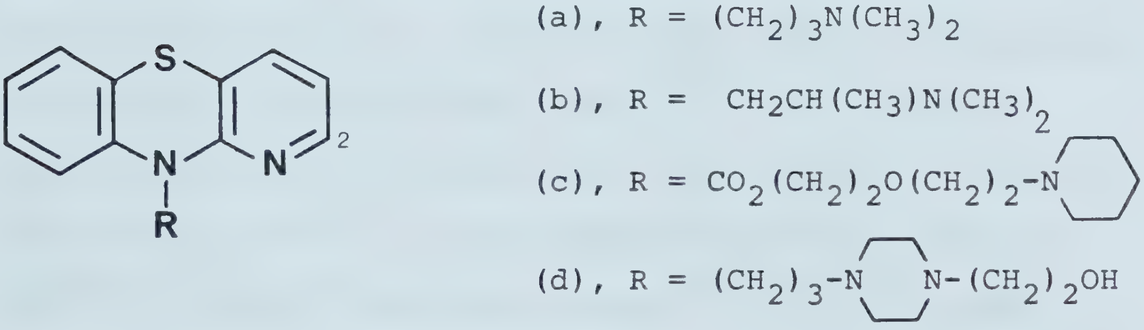
CIX



CX

1.10.0.0.0 The pharmacology of azaphenothiazines.

The pharmacology of azaphenothiazines has been reviewed[266,274]. The marked medicinal properties of a number of 1-azaphenothiazine analogues has encouraged further investigations into azaphenothiazine chemistry and pharmacology. Prothipendyl (CXI-a) is an antihistaminic which is more potent than the corresponding phenothiazine analogue[266]. Isothipendyl (CXI-b), pervetral (XCI-c) and pipazethate (CXI-d) are employed as antihistaminic, antiemetic and antitussive agents, respectively. In contrast to chlorpromazine[275], the analagous introduction of chorine at the C-2 position of CXII results in a marked reduction of pharmacological activity.



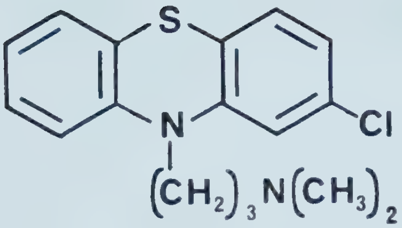
(a), R = $(CH_2)_3N(CH_3)_2$

(b), R = $CH_2CH(CH_3)N(CH_3)_2$

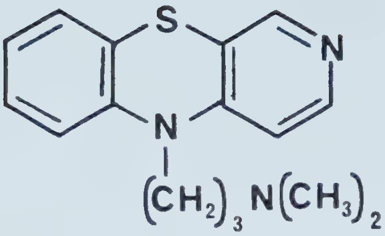
(c), R = $CO_2(CH_2)_2O(CH_2)_2$-N

(d), R = $(CH_2)_3$-N N-$(CH_2)_2OH$

CXI

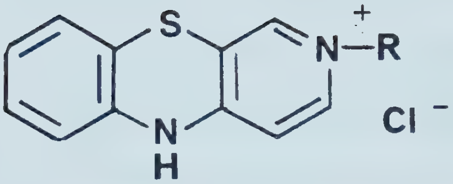


Chlorpromazine

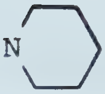


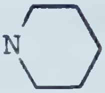
CXII

The corresponding 3-azaphenothiazine analogue of CXI-a, 10-(3-dimethylaminopropyl)-3-azaphenothiazine (CXII), has been patented for antidepressant properties[276] despite the fact that its dihydrochloride salt is essentially inactive as a tranquilizing agent[270]. The antihistaminic properties associated with CXI-a and CXI-b are not exhibited by CXII[277]. The azaphenothiazinium chloride (CII) is a potent hypotensive agent[270,278,279]. Other related phenothiazinium salts CXIII-a, CXIII-b and CXIII-c also reduce high arterial blood pressure but the effects are less marked and more transient than those observed with CII[270].



CXIII

(a), R = $(CH_2)_3$-N 

(b), R = $(CH_2)_2$-N 

(c), R = $(CH_2)_2NH_2$

2.0.0.0.0 OBJECTS OF RESEARCH

The [3 + 2]cycloaddition reaction of dienophiles with alkenes and alkynes is an interesting and simple method for the preparation of novel heterocycles with potential pharmacological activities. The addition of organic azides to N-unsubstituted- and N-substituted-1,2-dihydropyridines[148-150] affords fused aziridine-tetrahydropyridine bicyclics possessing analgesic and antimicrobial properties[150]. It was therefore of interest to extend the scope of this reaction to include the 1,3-dipolarcycloaddition reaction of selected organic azides with enamines such as N-substiuted-1,4-dihydropyridines. The products obtained from these reactions would be fused triazoline-tetrahydropyridine and/or aziridine-tetrahydropyridine bicyclics. In addition, simple cyclic enamines such as N-alkyl-1,2,3,4-tetrahydropyridines would be expected to undergo a cycloaddition reaction with organic azides to give either fused aziridine-piperidine bicycles and/or 2- or 3-substituted piperidylidenes. The analgesic and antimicrobial activities of these compounds would be of interest.

Elaboration of the fused pyridine ring system present in the pharmacologically active 10-substituted-10H-pyrido[3,2-b][1,4]benzothiazines using organolithium reagents has been investigated[271,272]. It was therefore also of interest to investigate the synthesis of other reduced pyridobenzothiazines by reduction of 10-substituted-10H-

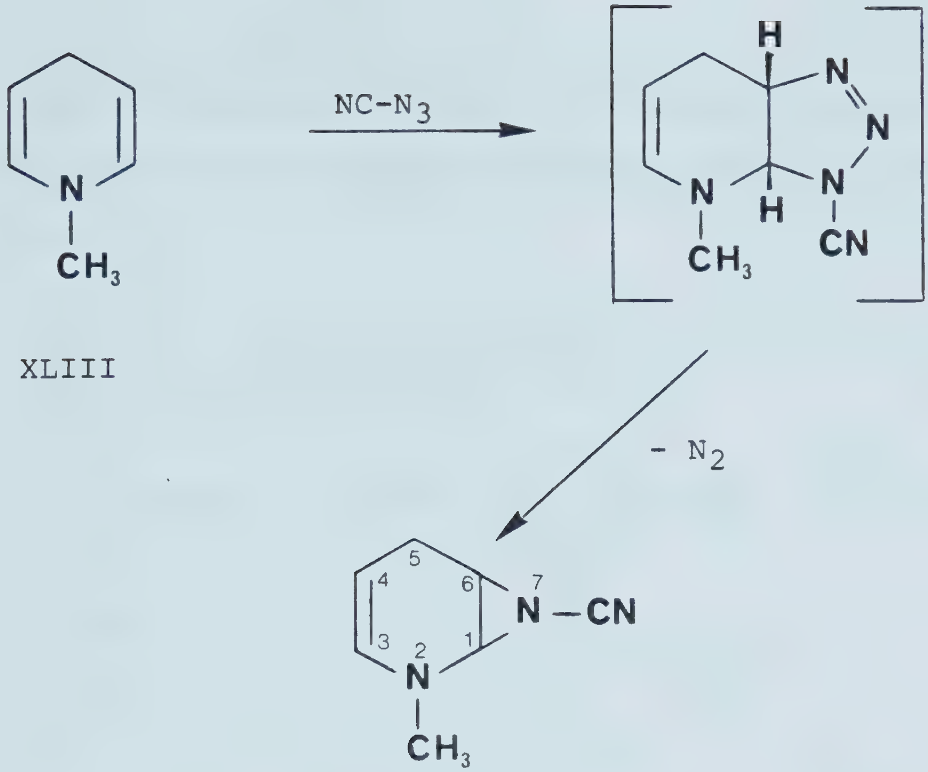
pyrido[3,4-b][1,4]benzothiazines by a variety of reduction procedures. It was hoped that these reduction products would exhibit pharmacological activity themselves or perhaps act as pro-drugs.

3.0.0.0.0 DISCUSSION

3.1.0.0.0 Reaction of 1-methyl-1,4-dihydropyridine with organic azides. Synthesis of 2-methyl-2,7-diazabicyclo[4.1.0]hept-3-enes.

The enamine 1-methyl-1,4-dihydropyridine (XLIII) was prepared by lithium aluminum hydride reduction of 1-ethoxycarbonyl-1,4-dihydropyridine in refluxing ether[94]. Subsequent reaction of an ethereal solution of XLIII with one molar equivalent of cyanogen azide in acetonitrile afforded 2-methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (CXIV) in 99% yield.

The bicyclic CXIV arises from the 1,3-dipolarcycloaddition reaction of cyanogen azide with the enamine carbon-carbon double bond. The most probable mechanism for the cycloaddition is shown by equation (1). This reaction involves the formation of an unstable triazoline intermediate which undergoes decomposition and concomitant loss of nitrogen to produce the bicyclic product CXIV. If the reaction pathway is under electronic control, the nitrogen atom bearing the cyano group should be directed to the carbon of the enamine bond bearing the ring nitrogen(1)[280]. Hermes and Marsh have demonstrated that the triazolines of strained cyclic olefins decompose primarily to aziridines[147]. Decomposition of the triazoline adduct therefore occurs as predicted(1).



XLIII

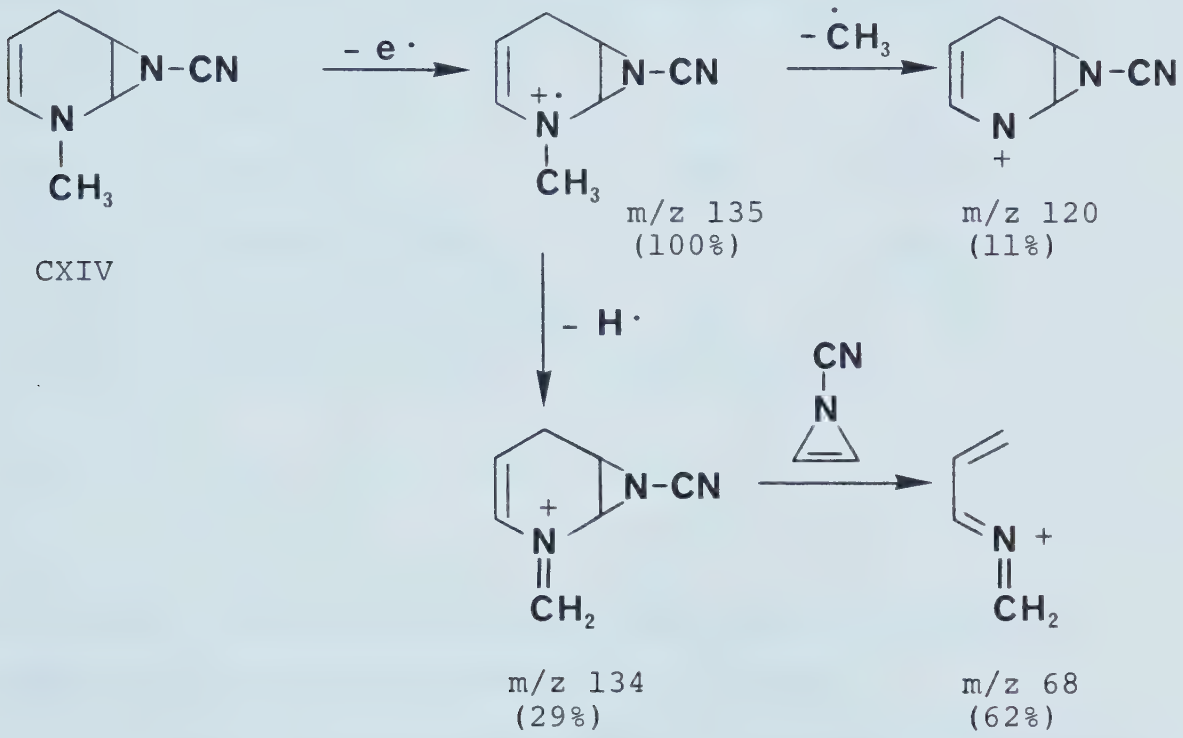
CXIV

(1)

The nmr spectrum(δ) of CXIV exhibits a 2H multiplet at 2.5 due to the C_5-H, a 2H multiplet at 3.15 attributed to the C_1-H and C_6-H, a 3H singlet at 3.3 due to the methyl, a 1H multiplet ascribed to the C_4-H at 5.5 and a doublet ($J_{3,4}$=8Hz) of doublets ($J_{3,5}$=2Hz) of doublets ($J_{3,5}$=2Hz) at 6.1 assigned to the C_3-H. The infrared spectrum shows the presence of a cyano group (2190 cm^{-1}) and an olefinic bond (1665 cm^{-1}). The mass spectrum of CXIV exhibits a molecular ion at m/z 135(Exact mass calc'd for $C_7H_9N_3$: 135.0796; found (high resolution ms): 135.0797). Fragmentation of the molecular ion occurs by two major pathways (Scheme V). Loss of a methyl radical gives rise to a peak at m/z 120($C_6H_6N_3^+$). The peak at m/z 68($C_4H_6N^+$) arises from the loss of a hydrogen

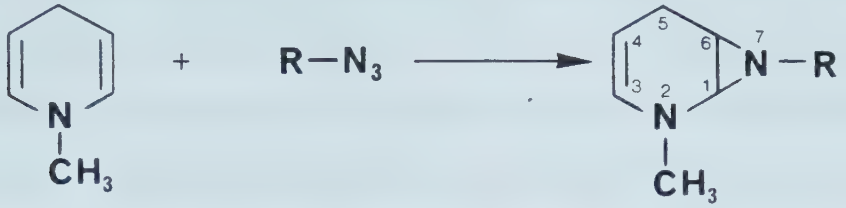
radical from the molecular ion followed by the expulsion of N-cyanoazirine via a retro Diels-Alder fragmentation mechanism.

Scheme V: Major fragmentations of 2-methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (CXIV).



The reaction of a variety of sulfonyl azides with 1-methyl-1,4-dihydropyridine (XLIII) was also investigated. The resulting 2-methyl-7-substituted-2,7-diazabicyclo[4.1.0]-hept-3-enes obtained following the 1,3-dipolarcycloaddition reaction of XLIII with cyanogen and sulfonyl azides are summarized in Table I. The nmr, ir and mass spectral data of CXV to CXVIII inclusive are in accordance with the assigned

Table I: Synthetic data for 2-methyl-7-substituted-2,7-diazabicyclo[4.1.0]hept-3-enes.



Compd	R	yield(%)	mp(°C)
CXIV	CN	99	67-69
CXV	CH_3SO_2	96	70-72
CXVI	$PhSO_2$	98	57-59
CXVII	$4\text{-}NH_2\text{-}C_6H_4\text{-}SO_2$	97	188-190
CXVIII	$4\text{-}CH_3CONH\text{-}C_6H_4\text{-}SO_2$	94	177-179

structures. Elemental analyses (C, H and N) of all compounds in Table I were within 0.4% of theory.

The 1,3-dipolarcycloaddition reaction of 1-methyl-1,4-dihydropyridine (XLIII) with organic azides, other than cyanogen- or sulfonyl-azides did not proceed. For example, the addition of an etheral solution of benzoyl azide to one mole equivalent of XLIII in ether afforded only starting azide and intractable material. Similar results were obtained for the reactions of methoxycarbonyl azide and phenyl azide with XLIII. The electron withdrawing properties of cyano and sulfonyl groups increase the electrophilic character of the azide functionality. Cyanogen and sulfonyl-

azides both exhibit enhanced reactivity with the electron rich enamine double bond. Methoxycarbonyl azide which is generally considered an activated azide apparently is not reactive enough to undergo a cycloaddition reaction with 1-methyl-1,4-dihydropyridine.

Reaction of 1-ethoxycarbonyl-1,4-dihydropyridine with one equivalent of methanesulfonyl azide at 25°C for 36 h yielded only starting materials. An electron attracting ethoxycarbonyl moiety present on the ring nitrogen reduces the nucleophilic character of the enamine double bond. The decreased reactivity of the olefinic bond present in 1-ethoxycarbonyl-1,4-dihydropyridine precludes the 1,3-dipolarcycloaddition reaction with organic azides.

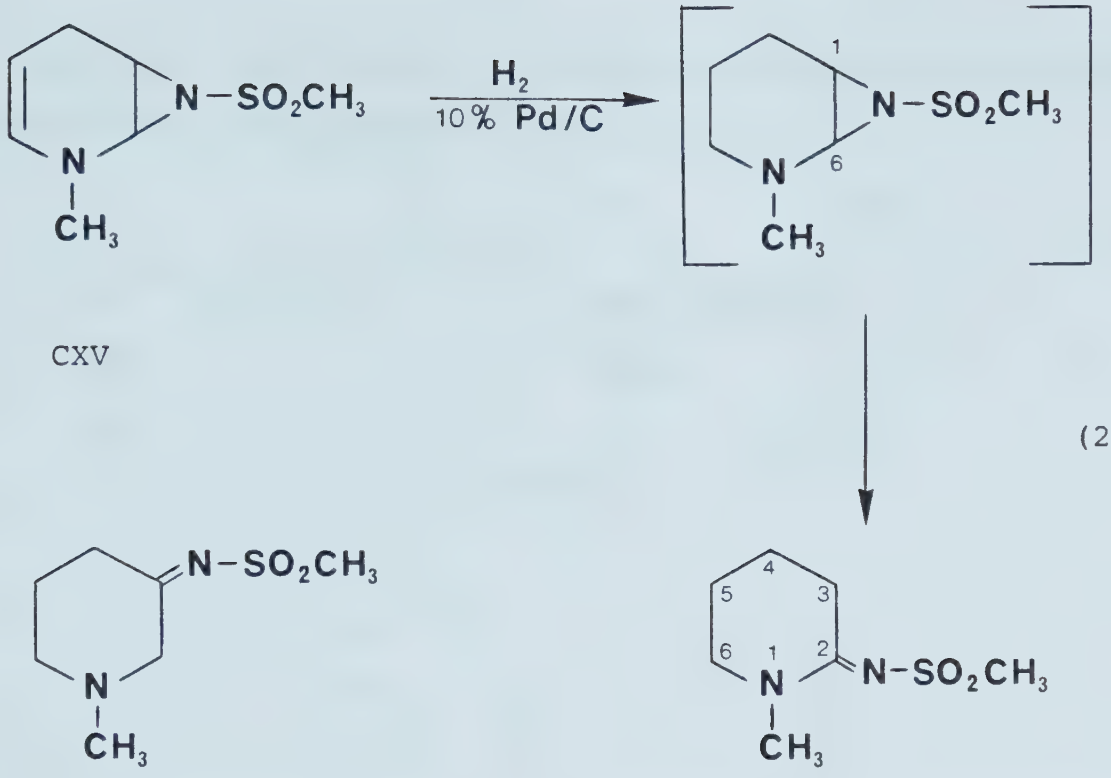
The 1,3-dipolarcycloaddition reaction of XLIII with five mole equivalents of methanesulfonyl azide afforded only 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]-hept-3-ene (CXV). A product resulting from addition of methanesulfonyl azide across both the C_2-C_3 and C_5-C_6 double bonds of XLIII was not formed. In addition, CXV did not react further with methanesulfonyl azide. The addition of methanesulfonyl azide to the C_3-C_4 olefinic bond of CXV may be hindered by steric effects and/or the enamine bond may be deactivated electronically. A Dreiding model of CXV indicates that methanesulfonyl azide may be hindered in its approach to the olefin by the aziridine N-substituent. In addition the fused aziridine ring of CXV may cause

sufficient deactivation thereby preventing the enamine from reacting.

3.2.0.0.0 Hydrogenation of 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXV). Synthesis of 1-methylpiperidylidene-2-methanesulfonamide (CXIX).

The hydrogenation of 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXV) with 10% palladium on charcoal in 95% ethanol using hydrogen gas at 30 psi afforded 1-methylpiperidylidene-2-methanesulfonamide (CXIX) in 98% yield. The formation of CXIX probably occurs by the reduction of the olefinic bond of CXV followed by aziridine ring opening and migration of the C_1-H (2). Opening of the aziridine ring intermediate and migration of the C_6-H would afford a 3-substituted piperidylidene. The nmr, ir and mass spectral data for the product obtained from the reduction of CXV supports structure CXIX rather than CXX.

The nmr spectrum(δ) of CXIX exhibits a 4H multiplet at 1.85 due to the C_4-H and C_5-H, an 8H multiplet at 3.1 assigned to the C_3-H, SO_2CH_3 and NCH_3 and a 2H multiplet at 3.4 due to C_6-H. The structure CXX is unlikely since a C_2-H would absorb further downfield than the observed 3.4 δ . The infrared spectrum of CXIX shows the presence of an imino group at 1590 cm^{-1}. The mass spectrum of CXIX exhibits a molecular ion at m/z 190 (Exact mass calc'd for



CXV

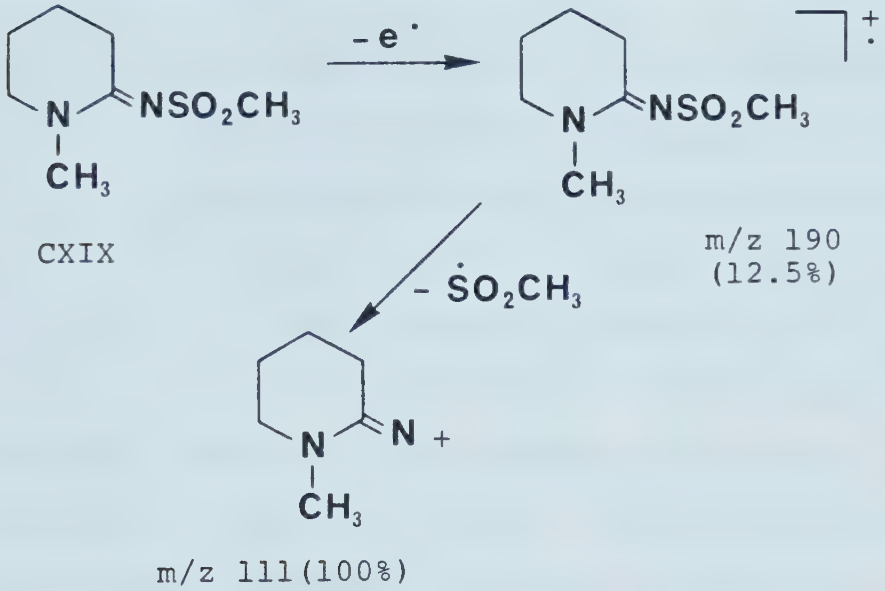
(2)

CXX

CXIX

$C_7H_{14}N_2O_2{}^{32}S$: 190.0776; found (high resolution ms): 190.0787). The major fragmentation of the molecular ion occurs by loss of a methanesulfonyl radical giving rise to the base peak at m/z111 (Scheme VI).

Scheme VI: Mass spectral fragmentation of 1-methylpiperidylidene-2-methanesulfonamide (CXIX).



3.3.0.0.0 1,3-Dipolarcycloaddition reactions of 1-alkyl-1,2,3,4-tetrahydropyridines with cyanogen and sulfonyl azides.

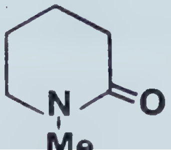
The 1,3-dipolarcycloaddition reaction of cyanogen and sulfonyl azides with 1,2-dihydropyridines afforded 2,7-diazabicyclo[4.1.0]hept-4-enes in high yield[148-150]. A similar cycloaddition reaction for 1-methyl-1,4-dihydropyridine has been discussed in the thesis earlier. The results indicate that cyclic enamines possessing a N-hydrogen(alkyl) substituent usually undergo 1,3-dipolarcycloaddition reactions with highly reactive organic azides. In a similar manner, cyanogen and sulfonyl azides would also be expected to undergo 1,3-dipolarcycloaddition reactions with N-alkyl-

1,2,3,4-tetrahydropyridines to afford 2,7-diazabicyclo-[4.1.0]heptanes and/or 2-(3-)piperidylidenes.

3.3.1.0.0 Reaction of 1-methyl-1,2,3,4-tetrahydropyridine with cyanogen and sulfonyl azides. Synthesis of 1-methylpiperidylidene-2-cyan(sulfon)amides.

The unstable enamine 1-methyl-1,2,3,4-tetrahydropyridine (LIII) was prepared by isomerization of 1-methyl-1,2,3,6-tetrahydropyridine using potassium *tert*-butoxide[140]. Subsequent reaction of an ethereal solution of LIII with a slight molar excess of cyanogen azide in acetonitrile gave 1-methylpiperidylidene-2-cyanamide (CXXI) as a white solid in 81% yield. Ritchie and Rosenberger[151] reported that reaction of 1,6-dimethyl-1,2,3,4-tetrahydropyridine with tosyl azide afforded only 1,3-dimethylpiperidylidene-2-tosylsulfonamide. The reaction of LIII with cyanogen azide occurred in a similar manner to give CXXI. No product corresponding to 1-methylpiperidylidene-3-cyanamide was obtained.

Additional evidence for the formation of 2-substituted piperidylidenes from the reaction of LIII with organic azides was obtained by the acid hydrolysis of 1-methylpiperidylidene-2-cyanamide (CXXI)[281]. Treatment of CXXI with 10% aqueous sulfuric acid in methanol gave 1-methyl-2-piperidone (CXXII) in 55% yield. The ir and nmr spectra of CXXII were identical to those of an authentic



CXXII

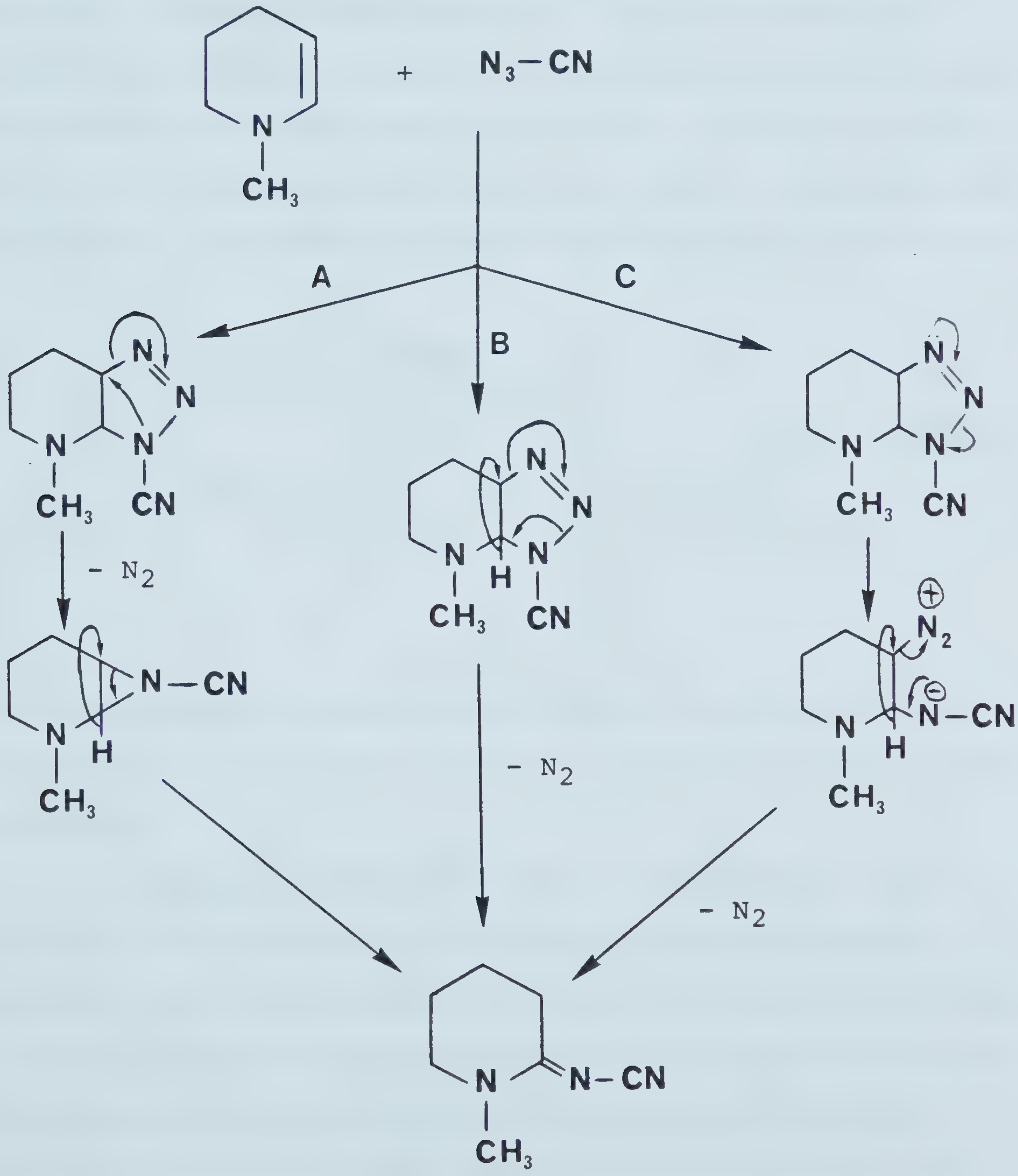
sample. The formation of CXXII must arise from the precursor 1-methylpiperidylidene-2-cyanamide (CXXI). Acid hydrolysis of 1-methylpiperidylidene-3-cyanamide would have given rise to 1-methyl-3-piperidone.

The 1,3-dipolarcycloaddition reaction of LIII with cyanogen azide may proceed by a number of mechanisms as illustrated by Scheme VII. All of the plausible pathways involve the loss of nitrogen from an unstable triazoline intermediate.

Pathway A involves the initial formation of an unstable triazoline intermediate. The triazoline adduct could then lose nitrogen to give an aziridine-piperidine bicyclic which undergoes a C-1 hydrogen migration to afford CXXI. Evidence supporting this mechanism involves reaction of 1-methyl-1,4-dihydropyridine with cyanogen azide. The product from this reaction is the aziridine bicycle 2-methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (CXIV). The formation of CXIV likely occurs in a manner similar to that illustrated in Pathway A. In addition, hydrogenation of 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXV) affords 1-methylpiperidylidene-2-methanesulfonamide (CXIX). The formation of CXIX must involve an intermediate similar to structure A-1 along Pathway A.

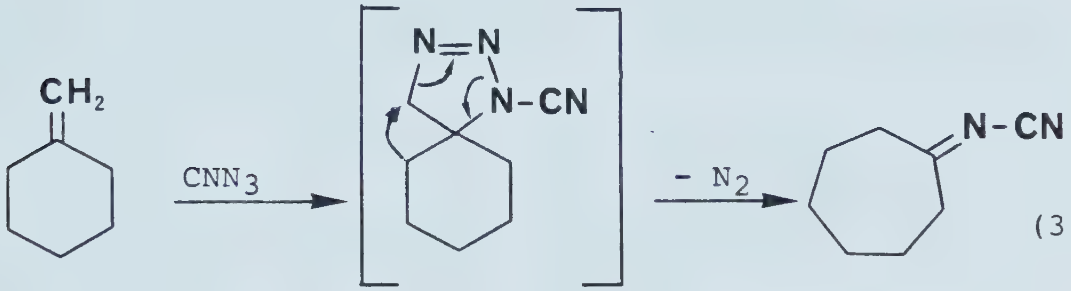
Pathways B and C are also possible explanations for the formation of CXXI. Ritchie and Rosenberger[151] favored a mechanism similar to pathway B to explain the formation

Scheme VII: Possible mechanisms for the formation of 1-methylpiperidylidene-2-cyanamide (CXXI).



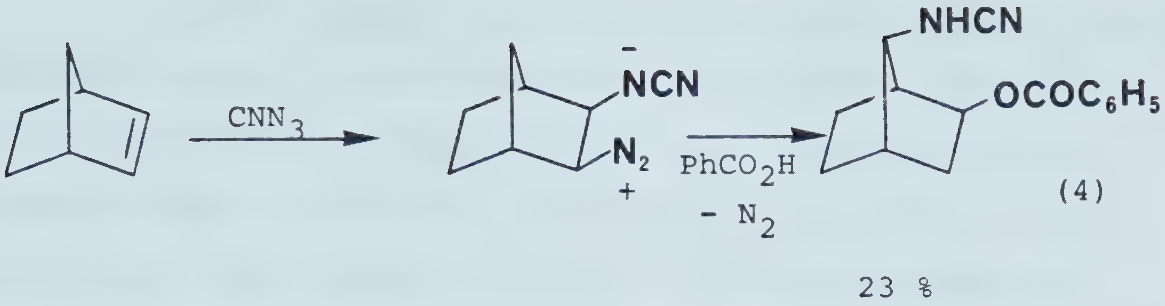
CXXI

of 1,3-dimethylpiperidylidene-2-tosylsulfonamide from the reaction of 1,6-dimethyl-1,2,3,4-tetrahydropyridine and tosyl azide. This work was discussed earlier in the introduction. McMurray and Coppolino[282] favor a concerted mechanism similar to pathway B to explain the formation of the product obtained from the reaction of methylene cyclohexane with cyanogen azide which gave only a ring expansion product(3). The seven membered ring could also arise from the zwitterionic intermediate as shown by pathway C. This mechanism is less likely since some aziridine would also be expected.



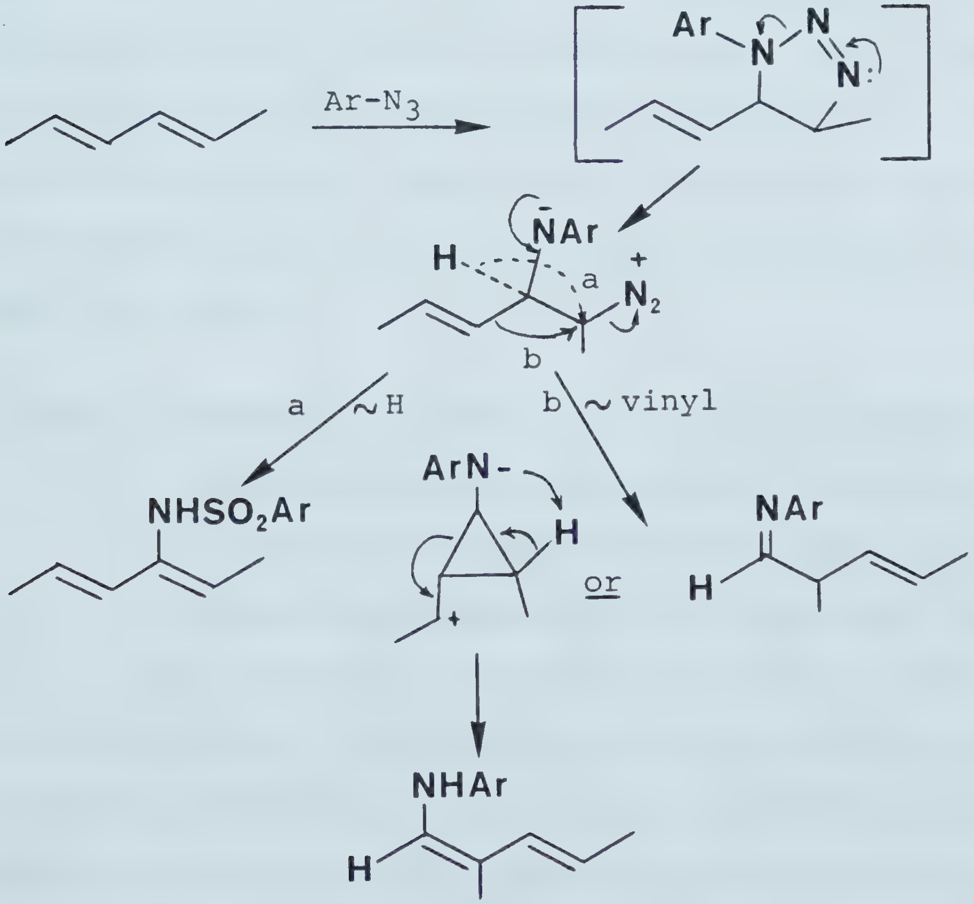
(3)

Hermes and Marsh[147] favor a zwitterionic intermediate for the addition of cyanogen azide to olefins. A possible ionic intermediate has been intercepted in the reaction of cyanogen azide with norbornene and benzoic acid(4). The benzoate is possibly formed by protonation of the diazonium cyanamide, loss of nitrogen and attack of the benzoate ion at the 7 position of the resulting carbonium ion. Abramovitch and co-workers[283] have investigated the



(4)

reaction of *p*-nitrobenzenesulfonyl azide with dienes. Addition of this azide to 1,5-hexadiene gives rise to three products whose formation is explained by a zwitterionic intermediate(5).



(5)

Ar = *p*-nitrobenzenesulfonyl

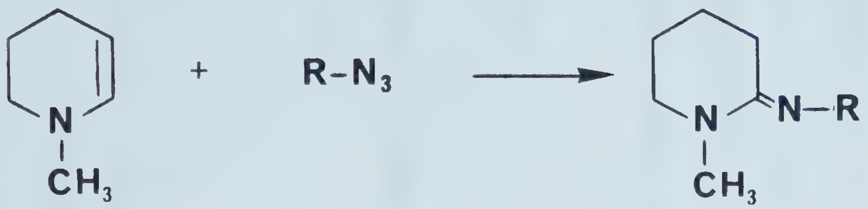
At the present time no one particular pathway can be favored nor can one be eliminated. Isolation or detection of intermediate A-1 along pathway A or the zwitterionic species shown in pathway C would result in a better understanding of the mechanism of the 1,3-dipolarcycloaddition of 1-methyl-1,2,3,4-tetrahydropyridine with organic azides.

The 1,3-dipolarcycloaddition reactions of cyanogen azide and a variety of sulfonyl azides using one mole equivalent of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) afforded 1-methylpiperidylidene-2-cyan(sulfon)amides as the sole product (see Table II). The 1-methylpiperidylidene-2-cyan(sulfon)amides listed in Table II are likely formed by one of the mechanisms outlined in Scheme VII. The nmr, ir spectra and elemental analyses (C, H and N) for the compounds listed in Table II are in accordance with their proposed structures.

3.3.2.0.0 Reduction of the nitro group of 1-methylpiperidylidene-2-(3-(2-)nitrophenyl)sulfonamide. Synthesis of 1-methylpiperidylidene-2-(3-(2)-aminophenyl)sulfonamide (CXXXIII) and (CXXXIV).

The procedure of Bovin[284] was used to reduce the nitro group of 1-methylpiperidylidene-2-(3-nitrophenyl)-sulfonamide (CXXVIII). A suspension of CXXVIII, 10% palladium on charcoal and 85% hydrazine hydrate in 95% ethanol was stirred at 25°C for 16 h to give 1-methylpiperidylidene-

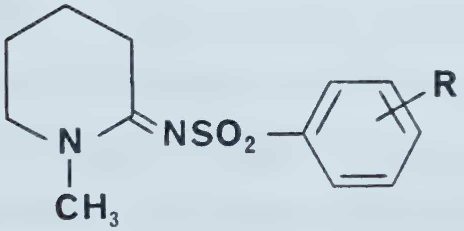
Table II: Synthetic data of 2-substituted-1-methylpiperidylidenes.



Compd	R	% yield	mp(°C)
CXIX	CH_3SO_2	82	130-131
CXXI	CN	81	98
CXXIII	$PhSO_2$	71	104
CXXIV	$4-CH_3-C_6H_4-SO_2$	78	110-111
CXXV	$4-Cl—C_6H_4-SO_2$	73	106-107
CXXVI	$4-MeO-C_6H_4-SO_2$	70	103-105
CXXVII	$4-NO_2-C_6H_4-SO_2$	65	147-148
CXXVIII	$3-NO_2-C_6H_4-SO_2$	65	136-137
CXXIX	$2-NO_2-C_6H_4-SO_2$	67	126-127
CXXX	$4-CH_3CONH-C_6H_4-SO_2$	79	222-223
CXXXI	$4-NH_2-C_6H_4-SO_2$	89	187-188
CXXXII	$3-pyridyl-SO_2$	79	96-97

2-(3-aminophenyl)sulfonamide (CXXXIII) in 76% yield. The assigned structure is in agreement with its nmr, ir spectra and elemental analysis (C, H and N).

Reduction of the nitro functionality of 1-methylpiperidylidene-2-(2-nitrophenyl)sulfonamide (CXXIX) required more vigorous conditions than required for the 3-nitro group of CXXVIII. The steric interaction of the nitro- and sulfonyl groups of CXXIX partially inhibits the palladium-hydrazine complex from interacting with, and consequently reducing, the nitro functionality. A mixture of CXXIX, 10% palladium on charcoal and 95% hydrazine required heating at reflux for 24 h to afford 1-methylpiperidylidene-2-(2-aminophenyl)sulfonamide (CXXXIV). The ir, nmr and ms data confirm the assigned structure.



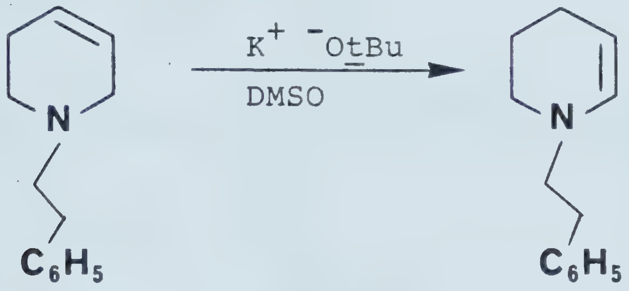
CXXXIII, R = 3-NH_2

CXXXIV, R = 2-NH_2

3.3.3.1.0 Synthesis of 1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine (CXXXV) and 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI).

One mole of 2-phenylethyl bromide and two moles of 1H-1,2,3,6-tetrahydropyridine were allowed to reflux using

toluene as solvent to yield 1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine (CXXXV) as a colorless oil. Subsequent isomerization of CXXXV with potassium tert-butoxide in anhydrous dimethyl sulfoxide for 48 h at 90°C afforded the unstable 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) in 93% yield (6).

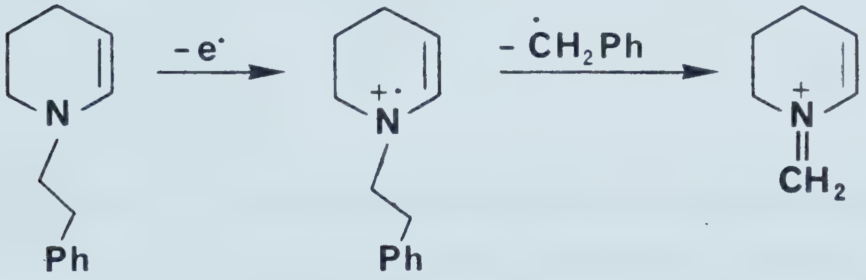


(6)

CXXXV CXXXVI

The nmr spectrum(δ) of CXXXV exhibited a 2H multiplet at 2.25 due to the C_3-H, a 6H multiplet at 2.7 attributed to the C_2-H and the N-ethyl, a 2H multiplet at 3.05 due to the C_6-H, a 2H multiplet at 5.7 assigned to C_4-H and C_5-H, and a broad 5H absorption at 7.2 assigned to the phenyl protons. The nmr spectrum(δ) of CXXXVI is significantly different from that of CXXXV. The C_3-H and C_4-H both appear as 2H multiplets at 1.9 and 2.1 respectively, the 6H multiplet at 2.8 is assigned to C_2-H and N-ethyl, the 2H multiplet at 5.7 is due to C_5-H and C_6-H, and a 5H multiplet at 7.2 is attributed to the phenyl protons. The high resolution mass spectrum of CXXXV did not display a molecular ion,

however, the chemical ionization mass spectrum exhibited the pseudomolecular ion $(M + 1)^+$ at m/z 188. The 1,2,3,4-tetrahydropyridine CXXXVI exhibits a molecular ion at m/z 187 (Exact mass calc'd for $C_{13}H_{17}N$: 187.1361; found (high resolution ms): 187.1359). Loss of a benzyl radical from the molecular ion of CXXXVI gives rise to the base peak at m/z 96 ($C_6H_{10}N^+$)(7).



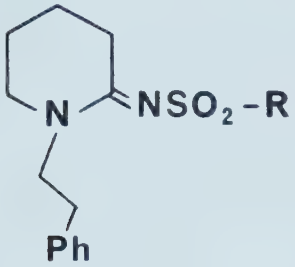
(7)

CXXXVI　　m/z 187(6%)　　m/z 96(100%)

3.3.3.2.0 Reaction of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) with aromatic sulfonyl azides.

The reaction of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) with aromatic sulfonyl azides was performed in a manner similar to the reaction of 1-methyl-1,2,3,4-tetrahydropyridine with azides (see 3.3.1.0.0). Thus reaction of 4-chloro-, 4-amino- and 3-pyridylsulfonyl azide with CXXXVI gave 1-(2-phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII), 1-(2-phenylethyl)-piperidylidene-2-(4-aminophenyl)sulfonamide (CXXXVIII) and 1-(2-phenylethyl)piperidylidene-2-(3-pyridyl)sulfonamide (CXXIX) in 25, 29 and 23% yield respectively. Unreacted azide was also detected in all reactions. The nmr, ir

spectra and elemental analyses (C, H and N) of CXXXVII, CXXXVIII and CXXXIX are in accordance with their assigned structures.



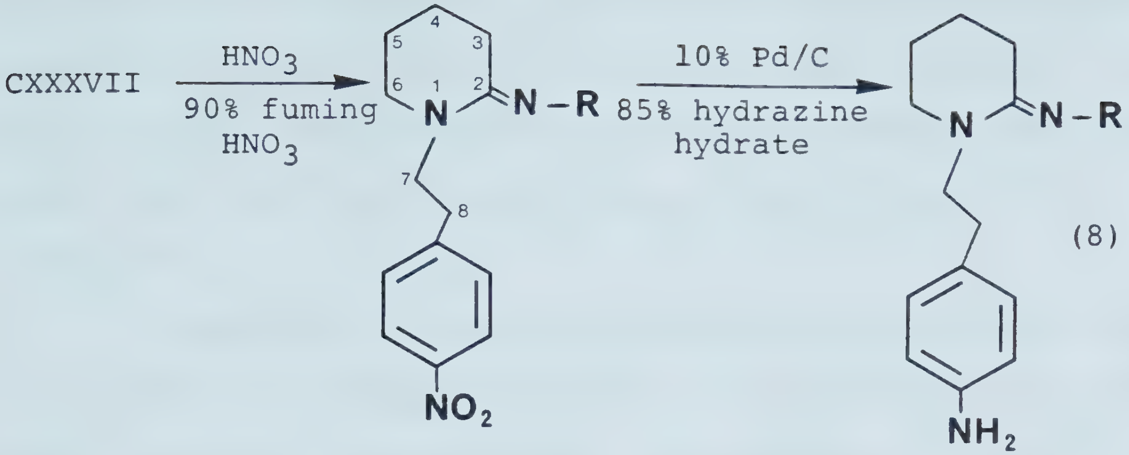
CXXXVII, R = C_6H_4-4-Cl

CXXXVIII, R = C_6H_4-4-NH_2

CXXXIX, R = 3-pyridyl

3.3.3.3.0 Synthesis of 1[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXL) and 1-[2-(4-aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXLI).

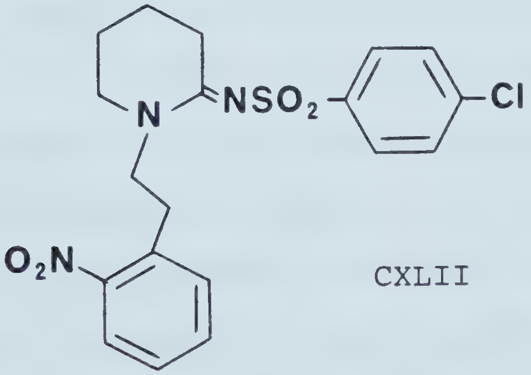
Replacement of the N-methyl substituent in narcotic analgesics by a N-phenylethyl or N-(4-aminophenyl)ethyl group often results in an increased analgesic activity. For example, replacement of the N-methyl group in morphine by an N-phenylethyl substituent results in a fourteen fold increase in analgesic potency[285]. A compound of potential interest as an analgesic in the piperidylidene series is the N-(4-aminophenyl)ethyl compound CXLI. The simple reaction sequence used to prepare CXLI is shown in equation (8). Nitration of 1-(2-phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII) was accomplished by reacting CXXXVII with concentrated nitric acid and 90% fuming nitric



CXL CXLI

R = SO_2-C_6H_4-4-Cl

acid at 25°C. The only product isolated from the reaction mixture was 1-[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXL) in 61% yield. No product corresponding to the structure CXLII was detected.



CXLII

The nmr spectrum(δ) of CXL exhibited a 4H multiplet at 1.75 due to the C_4-H and C_5-H, a 6H multiplet at 3.2 assigned to the C_3-H, C_6-H and C_7-H or C_8-H, a 3H triplet ($J_{7,8}$=7Hz) at 3.68 due to the C_7-H or C_8-H, and two sets of 4H multiplets at 7.4 and 8.0 attributed to the

orthochlorophenyl protons, orthomethylenephenyl protons and orthosulfonylphenyl protons, orthonitrophenyl protons, respectively. The ir spectrum shows the presence of an imino group (1570 cm^{-1}) and a nitro group (1540 cm^{-1} and 1350 cm^{-1}).

Reduction of the nitro group in CXL to afford 1-[2-(4-aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXLI) was effected using the procedure of Bovin[284] (see 3.3.2.0.0). The assigned structure for CXLI is in agreement with its nmr, ir and ms data.

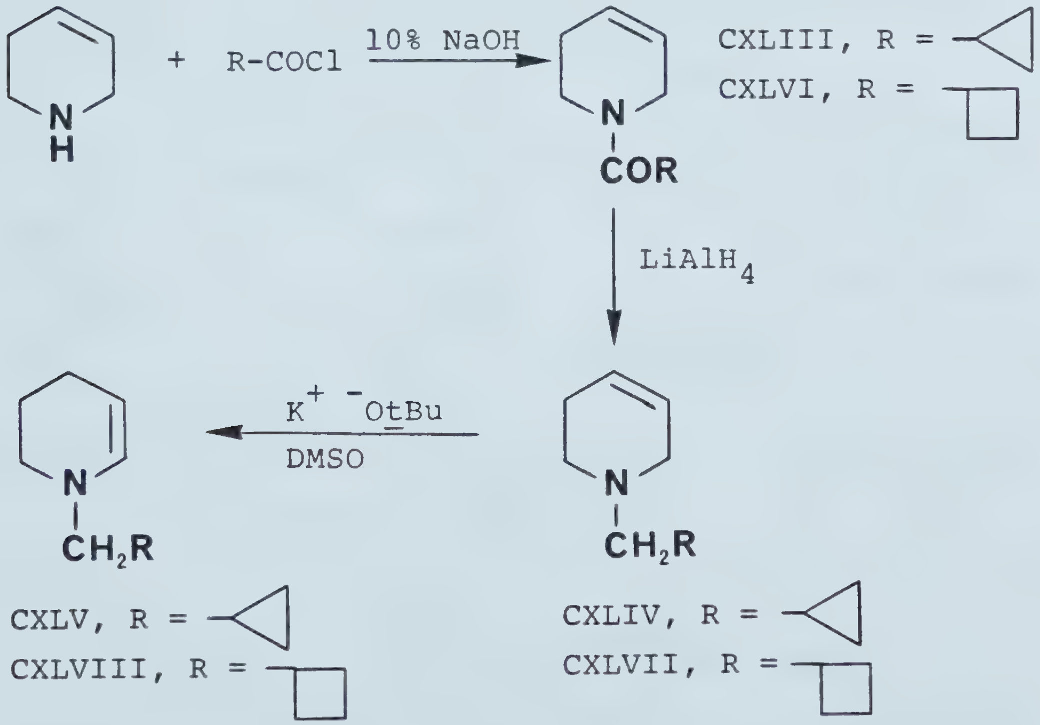
3.3.4.1.0 Synthesis of 1-cycloalkylmethyl(n-propyl, isobutyl)-1,2,3,4,-tetrahydropyridines.

Narcotic analgesic agonists usually require an N-methyl tertiary amino group as an important structural feature. In contrast, narcotic antagonists and partial agonists replace the N-methyl functionality by larger N-alkyl or N-cycloalkyl groups. Naloxone, buprenorphine and butorphanol are typical antagonists and partial agonists which were discussed in the introduction. It was therefore anticipated that replacement of the N-methyl group in the 1-methylpiperidylidene series by larger N-alkyl or N-cycloalkyl substituents would yield antagonists and/or partial agonists.

The synthesis of 1-cyclopropyl(cyclobutyl)methyl-1,2,3,4-tetrahydropyridines is presented in Scheme VIII. The

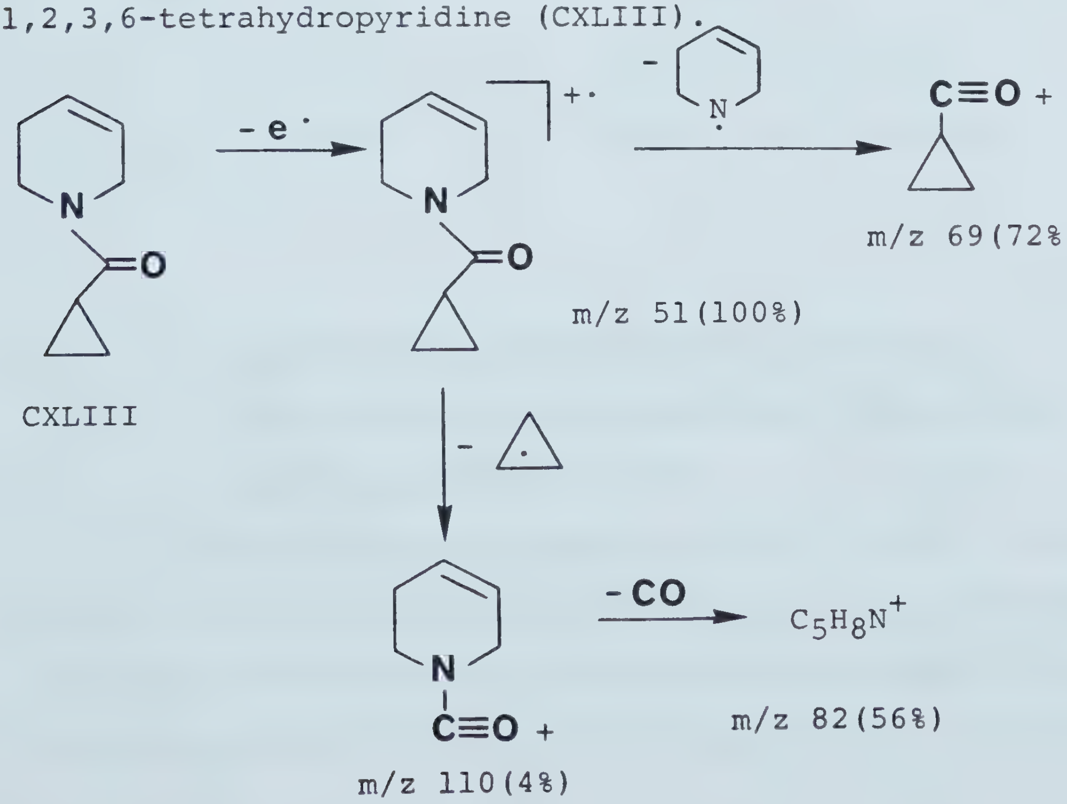
acylation of 1H-1,2,3,6-tetrahydropyridine using cyclopropanecarboxylic acid chloride in 10% aqueous sodium hydroxide afforded 1-cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII) as a colorless oil. The carbonyl functionality of CXLIII was reduced using lithium aluminum hydride in ether. The resulting product, 1-cyclopropylmethyl-1,2,3,6-tetrahydropyridine (CXLIV), was treated with potassium tert-butoxide in anhydrous dimethylsulfoxide to effect the synthesis of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV). 1-Cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII) was prepared in an analogous manner.

Scheme VIII: Preparation of 1-cyclopropyl(cyclobutyl)methyl-1,2,3,4-tetrahydropyridine (CXLV and CXLVIII).

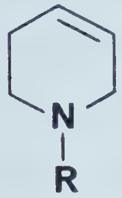


The nmr, ir and ms data for the compounds shown in Scheme VIII are consistent with their proposed structures. The mass spectrum of 1-cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII) exhibits a molecular ion at m/z 151 (Exact mass calc'd for $C_9H_{13}NO$: 151.0977; found (high resolution ms): 151.0999). Fragmentation of the molecular ion occurs by two major pathways (Scheme IX). Loss of a 1,2,3,6-tetrahydropyridine radical gives rise to a peak at m/z 69($C_4H_5O^+$). The peak at m/z 82 ($C_5H_8N^+$) likely arises by the loss of a cyclopropyl radical followed by expulsion of carbon monoxide. Fragmentation of 1-cyclobutylcarbonyl-1,2,3,6-tetrahydropyridine (CXLVI) proceeds in a similar manner.

Scheme IX: Major fragmentations of 1-cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII).

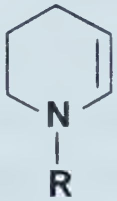


The preparation of 1-n-propyl(isobutyl)-1,2,3,4,-tetrahydropyridine (CLVI and CLVIII) was accomplished in a manner similar to the synthesis of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) (see 3.3.3.1.0). Thus reaction of 1H-1,2,3,6-tetrahydropyridine with 1-bromopropane afforded 1-n-propyl-1,2,3,6-tetrahydropyridine (CLV)[286] in 67% yield. Isomerization of the olefinic bond present in CLV using potassium tert-butoxide gave 1-n-propyl-1,2,3,4-tetrahydropyridine (CLVI) in 51% yield. The preparation of 1-isobutyl-1,2,3,4-tetrahydropyridine (CLVIII) was accomplished in an analogous manner.



CLV, R = n-propyl

CLVII, R = isobutyl



CLVI, R = n-propyl

CLVIII, R = isobutyl

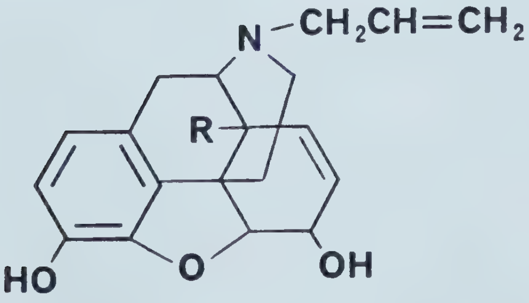
3.3.4.2.0 Reaction of 1-cycloalkylmethyl(n-propyl, isobutyl)-1,2,3,4-tetrahydropyridines with aromatic sulfonyl azides.

The addition of aromatic sulfonyl azides to one mole equivalent of 1-cycloalkylmethyl(n-propyl, isobutyl)-1,2,3,4-tetrahydropyridine was performed in manner previously outlined (see 3.3.1.0.0). The synthetic data for the

resulting 1-cycloalkylmethyl (n-propyl, isobutyl)piperidylidenes are listed in Table III. The nmr, ir spectra and the elemental analyses (C, H and N) for the products listed in Table III are in accordance with their proposed structures.

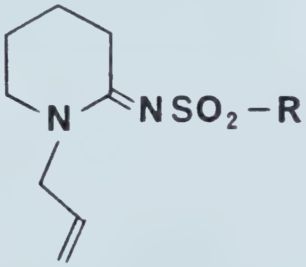
3.3.5.1.0 Preparation of 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI).

Narcotic analgesic antagonists and partial agonist-antagonists often feature an N-allyl group which is an important part of their structure. Compounds such as naloxone (LXVII) and nalorphine (LXX) have proven useful in research and clinical practise[287]. The preparation of N-allylpiperidylidenes is of interest due to their potential use as analgesic antagonists and agonist-antagonists. Pure narcotic antagonistic properties similar to naloxone or partial agonist-antagonist activities observed with nalorphine, would be expected if the N-allyl compound (CLXV) exerts its effect at a narcotic receptor.



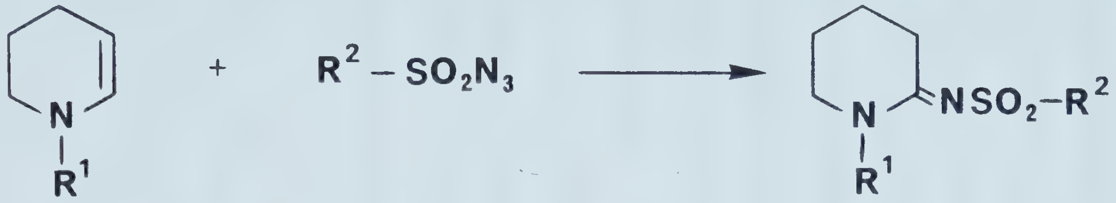
LXVII, R = OH

LXX, R =H



CLXV

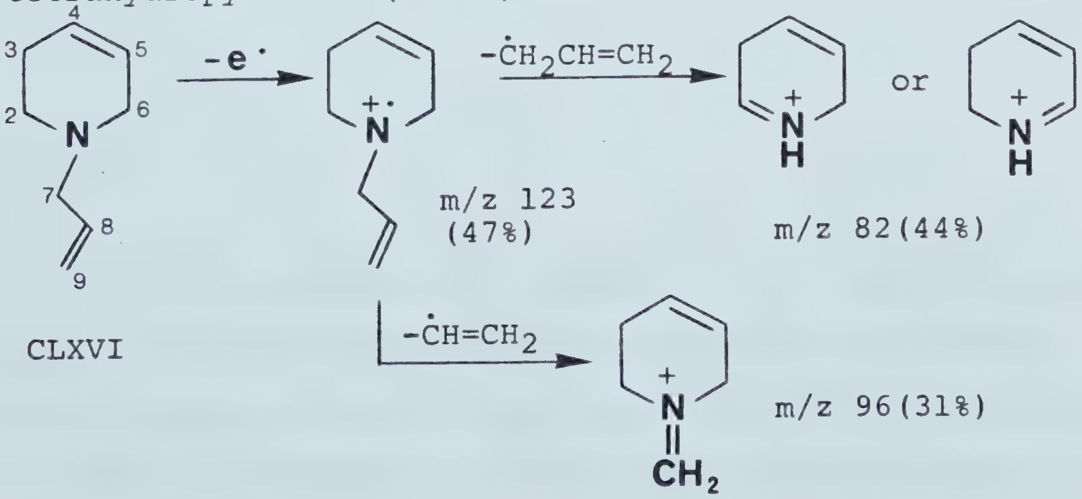
Table III: Synthetic data for the products from the reaction of 1-cycloalkylmethyl-(n-propyl, isobutyl)-1,2,3,4-tetrahydropyridines with aromatic sulfonyl azides.



Compd	R^1	R^2	yield(%)	mp(°C)
CIL	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	$4\text{-}Cl\text{-}C_6H_4$	56	114-115
CL	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	$4\text{-}NH_2\text{-}C_6H_4$	52	165
CLI	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	3-pyridyl	57	89
CLII	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	$4\text{-}Cl\text{-}C_6H_4$	68	113
CLIII	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	$4\text{-}NH_2\text{-}C_6H_4$	86	216-217
CLIV	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	3-pyridyl	91	56-57
CLIX	$CH_2CH_2CH_3$	$4\text{-}Cl\text{-}C_6H_4$	68	107-108
CLX	$CH_2CH_2CH_3$	$4\text{-}NH_2\text{-}C_6H_4$	65	178-179
CLXI	$CH_2CH_2CH_3$	3-pyridyl	64	109-110
CLXII	$CH_2CH(CH_3)_2$	$4\text{-}Cl\text{-}C_6H_4$	37	106
CLXIII	$CH_2CH(CH_3)_2$	$4\text{-}NH_2\text{-}C_6H_4$	49	184-185
CLXIV	$CH_2CH(CH_3)_2$	3-pyridyl	42	66-67

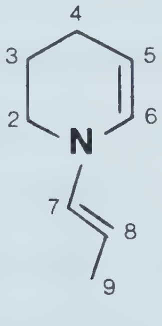
The dropwise addition of allyl bromide to an ethereal solution of 1H-1,2,3,6-tetrahydropyridine and pyridine at 0°C provided 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI) as a light yellow liquid in 62% yield. The nmr spectrum(δ) of CLXVI exhibits a 2H multiplet at 2.2 attributed to the C_3-H, a 2H triplet ($J_{2,3}$=6Hz) at 2.5 due to the C_2-H, a 4H multiplet at 3.0 assigned to the C_6-H and C_7-H, a 2H multiplet at 5.2 due to the C_9-H, and a 3H multiplet at 5.85 due to the C_4-H, C_5-H and C_8-H. The mass spectrum of CLXVI exhibits a molecular ion at m/z 123 (Exact mass calc'd for $C_8H_{13}N$: 123.1048; found (high resolution ms): 123.1046). The mass spectral fragmentation of the molecular ion is shown by Scheme X. Loss of an allyl radical gives rise to a peak at m/z 82 ($C_5H_8N^+$). The peak at m/z 96 ($C_6H_{10}N^+$) likely arises due to the loss of an ethylene radical from the molecular ion.

Scheme X: Major fragmentations of 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI).



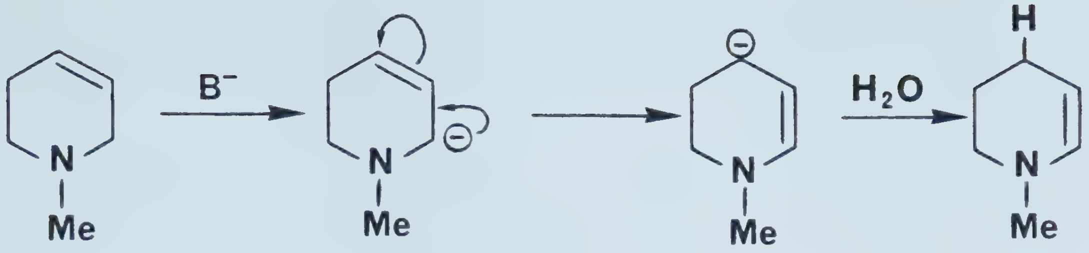
3.3.5.2.0 Synthesis of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine CLXVII).

Treatment of 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI) with potassium tert-butoxide in dimethylsulfoxide at 90°C for 48 h afforded E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII) as a brown liquid in 60% yield. The structure of CLXVII was consistent with the nmr spectrum. The nmr spectrum(δ) of CLXVII exhibits a 3H doublet ($J_{8,9}$=8Hz) at 1.60 attributed to the methyl, a 4H multiplet at 1.95 assigned to the C_3-H and C_4-H, a 2H multiplet at 3.16 due to the C_2-H, a 2H multiplet at 4.30 assigned to the C_5-H and C_8-H, and a 2H multiplet at 6.0 due to the C_6-H and C_7-H. The mass spectrum of CLXVII shows the presence of a molecular ion at m/z 123 (Exact mass calc'd for $C_8H_{13}N$: 123.1048; found (high resolution ms): 123.1047).



CLXVII

The reaction of 1-methyl-1,2,3,6-tetrahydropyridine with strong base under anhydrous conditions afforded 1-methyl-1,2,3,4-tetrahydropyridine (LIII)[140] (9). The initial step for the formation of LIII likely involves abstraction of

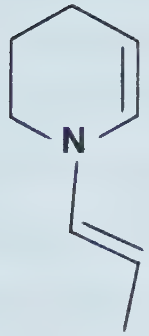


(9)

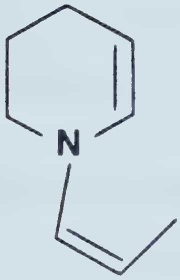
CLXVIII-a CLXVIII-b LIII

the active proton from the C-6 position of 1-methyl-1,2,3,6-tetrahydropyridine. Isomerization of the C-6 anion of CLXVIII-a to the C-4 position accompanied by double bond migration gives the intermediate CLXVIII-b. Treatment of CLXVIII-b with water affords LIII.

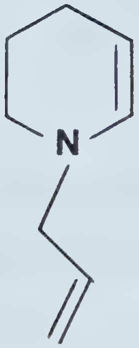
Theoretically, treatment of 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI) with strong base may lead to abstraction of the active hydrogens at the C-6 and/or C-7. Several unstable intermediates (CLXVII, CLXIX, CLXX, CLXXI, CLXXII) may be formed as a result of proton abstractions at the C_6 and/or C_7 positions. The nmr spectrum(δ) for the product obtained from the reaction of CLXVI with strong base shows the presence of a 3H doublet at 1.6 and a 2H multiplet at 6.0. The absorbance at 1.6 δ likely arises from a methyl group alpha to a carbon bearing a single hydrogen. The possible intermediate CLXX does not contain a methyl functionality or any group that would resonate as far upfield as 1.6 δ. The structure CLXX is therefore not a possible intermediate in the isomerization of CLXVI.



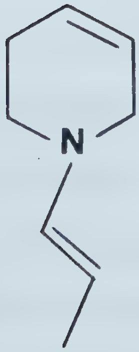
CLXVII



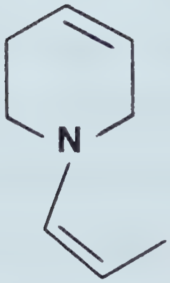
CLXIX



CLXX



CLXXI



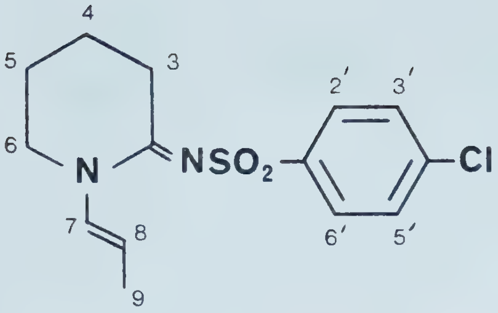
CLXXII

Olefinic protons normally absorb in the range of 4.0-5.5δ [288], however, the presence of a heteroatom alpha to an olefinic carbon causes a downfield shift of the proton attached to that olefinic carbon. A 2H multiplet at 6.0δ for the product arising from the isomerization of CLXVI indicates the presence of two olefinic protons on carbon atoms adjacent to the nitrogen. The isomeric intermediates CLXVII and CLXXII are the only structures which possess two olefinic protons capable of absorbing at 6.0 δ. Alkene coupling constants suggest the formation of CLXVII as the only product. The coupling constant of 15 Hz for the exocyclic double bond of the intermediate indicates that the E-isomer CLXVII was the only product formed.

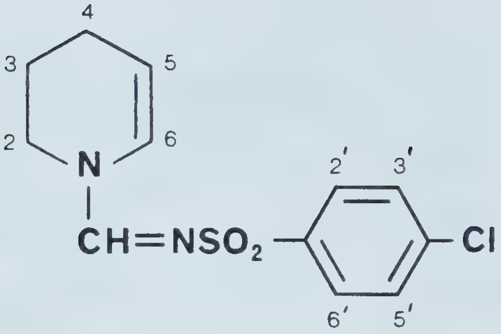
3.3.5.3.0 Reaction of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII) with 4-chlorobenzenesulfonyl azide.

The addition of 4-chlorobenzenesulfonyl azide to one equivalent of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII) gave E-1-(1-propenyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CLXXIII) and 1-(4-chlorophenyl)-sulfonimine-1,2,3,4-tetrahydropyridine (CLXXIV) in 43% and 20% yield respectively. The structures CLXXIII and CLXXIV were assigned on the basis of their spectral data.

Compound CLXXIII arises from the 1,3-dipolar-cycloaddition reaction of 4-chlorobenzenesulfonyl azide to



CLXXIII

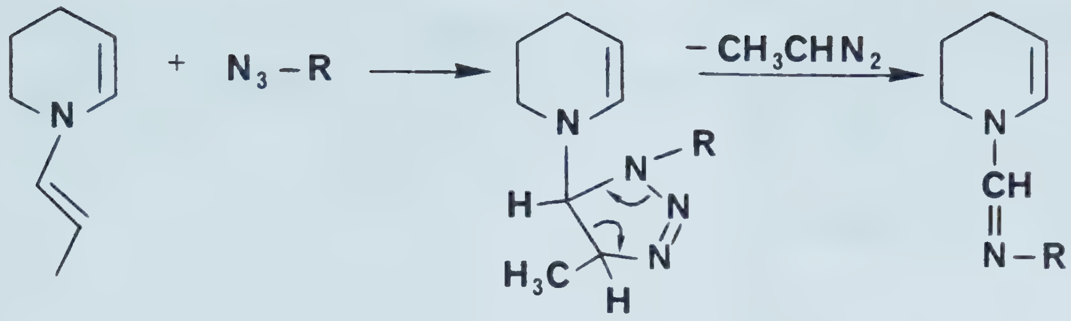


CLXXIV

the C_5-C_6 olefinic bond of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII). Decomposition of the intermediate triazoline could occur in a manner similar to that previously described for the reaction of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) with cyanogen azide.

The nmr spectrum(δ) of CLXXIII exhibits a 7H multiplet at 1.95 due to the C_4-H, C_5-H and terminal methyl, a 2H multiplet at 3.17 attributed to the C_3-H, a 2H multiplet at 3.55 due to the C_6-H, a 1H doublet ($J_{7,8}$=15Hz) of quartets ($J_{8,9}$=6Hz) at 5.30 ascribed to the C_8-H, a 1H doublet ($J_{7,8}$=15Hz) at 7.32 assigned to the C_7-H, a 2H doublet ($J_{2',3'}$=8Hz) at 7.43 due to the $C_{3'}$-H and $C_{5'}$-H, and a 2H doublet ($J_{2',3'}$=8Hz) at 7.92 attributed to the $C_{2'}$-H and $C_{6'}$-H). The ir spectrum of CLXXIII shows the presence of an imine group (1540 cm^{-1}) and olefinic group (1600 cm^{-1}). The coupling constants for the C_7-H and C_8-H (15 Hz) of CLXXIII are typical for an E-isomer[288].

A possible mechanism for the formation of 1-(4-chlorophenyl)sulfonimine-1,2,3,4-tetrahydropyridine (CLXXIV)

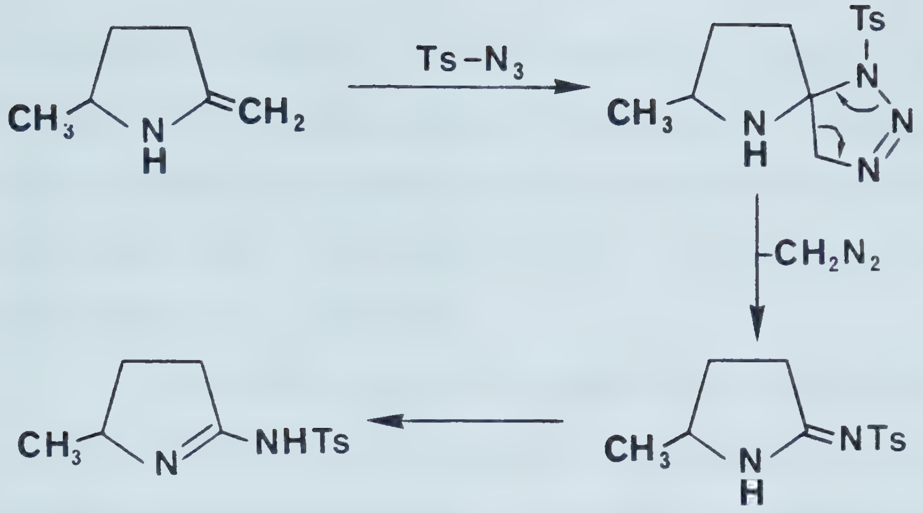


(10)

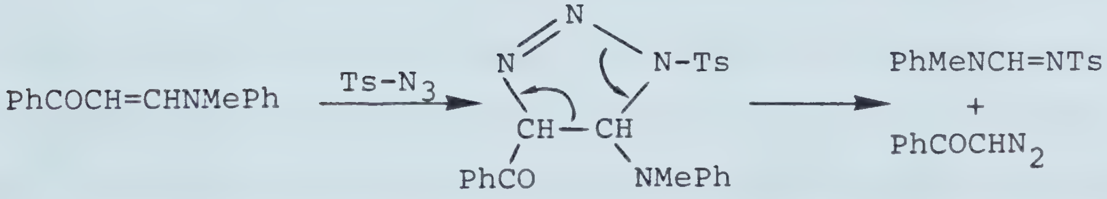
CLXXIV

R = $-SO_2C_6H_4-4Cl$

is shown in equation (10). The 1,3-dipolarcycloaddition of 4-chlorobenzenesulfonyl azide to the C_7-C_8 double bond of CLXVII initially could form an unstable triazoline intermediate. Decomposition of the triazoline ring yields CLXXIV and diazoethane. The nmr, ir and ms data support structure CLXXIV. Support for this mechanism is given in the reaction of 2,5-dimethyl-1-pyrroline with tosyl azide[151] (11). The amidine product is thought to arise by a mechanism similar to that postulated in equation (10). A similar mechanism is proposed in the formation of N-methyl-N-phenyl-N′-tosylsulfonylimine from the 1,3-dipolarcycloaddition of tosyl azide with 1-(N-methylaniline)-2-benzoylethylene[289] (12).



(11)



(12)

The nmr spectrum(δ) of CLXXIV exhibits a 4H multiplet at 2.06 due to the C_3-H and C_4-H, a 2H multiplet at 3.70 attributed to the C_2-H, a 1H multiplet at 5.3 assigned to the C_5-H, a 1H doublet ($J_{5,6}$=9Hz) at 6.42 due to the C_6-H, a 2H doublet ($J_{2',3'}$=9Hz) at 7.41 attributed to the $C_{3'}$-H and $C_{5'}$-H, a 2H doublet ($J_{2',3'}$=9Hz) at 7.84 due to the $C_{2'}$-H and $C_{6'}$-H, and a 1H singlet at 8.24 ascribed to

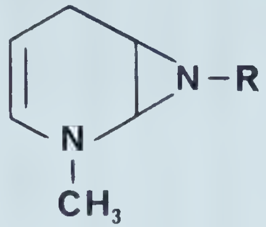
the methine proton. The ir spectrum of CLXXIV shows the presence of an imino group at 1600 cm^{-1}. The mass spectrum of CLXXIV displays a molecular ion at m/z 284 (Exact mass calc'd for $C_{12}H_{13}N_2O_2{}^{32}S^{35}Cl$: 284.0385; found (high resolution ms): 284.0385.

Reaction of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII) with two mole equivalents of 4-chlorobenzenesulfonyl azide also afforded the products CLXXIII and CLXXIV in 43% and 16% yield, respectively plus, some unreacted azide. No product arising from reaction of 4-chlorobenzenesulfonyl azide with the enamine functionality of either CLXXIII or CLXXIV was observed.

3.4.0.0.0 Pharmacological properties of 2-methyl-7-substituted-2,7-diazabicyclo[4.1.0]hept-3-enes.

The preparation of 2-methyl-7-substituted-2,7-diazabicyclo[4.1.0]hept-3-enes (CXIV-CXVIII) employing the 1,3-dipolarcycloaddition reaction of 1-methyl-1,4-dihydropyridine (XLIII) with organic azides was discussed earlier. Compounds CXIV-CXVIII were subjected to a broad spectrum pharmacological screen to assess pharmacological activity. The pharmacological properties found to be the most prominent for compounds CXIV-CXVIII were analgesic and antientamoebic activities (Table IV). The entire series of compounds CXIV-CXVIII were found to be active against *Entamoeba histolytica* with MIC's of less than 10 μg/ml using the Tube

Table IV: Pharmacological data for 2-methyl-2,7-diazabicyclo[4.1.0]hept-3-enes.



Compd	R	Analgesic act., inhib act. on phenylquinone writing[a] dose(mg/kg sc)	%inhib	min inhib conc (MIC) μg/mL of medium ofeach compd that inhibited growth of *E. histolytica*
CXIV	CN	64	86	< 10
CXV	SO_2CH_3	128	50	< 10
CXVI	SO_2Ph	64	92	< 10
CXVII	SO_2-C_6H_4-4-NH_2	19	50	< 10
CXVIII	SO_2-C_6H_4-4-$NHCOCH_3$	128	95	< 10
Aspirin™		50	50	

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[a] Phenylquinone writhing test in mice[290].

dilution technique (see experimental). The 2,7-diazabicyclo[4.1.0]hept-3-enes however were inactive against Trichomonas vaginalis at a dose of greater than 50 μg/ml using the same test. On the other hand compounds CXIV-CXVIII demonstrated weak or no antimicrobial properties.

The bicyclics CXIV-CXVII shown in Table IV demonstrated significant analgesic properties in the mouse phenylquinone writhing test[290]. The detailed procedure for the phenylquinone writhing test is given in the experimental. Briefly, a dose of the test compound dissolved in isotonic saline is injected subcutaneously to a set of five mice. After thirty min the pain inducing agent, 0.03% phenylbenzoquinone, is administered intraperitoneally. Ten min later, the mice are counted for writhing responses over a ten min period. The average number of writhes is compared to a set of ten mice who received only phenylbenzoquinone. The compound containing a methanesulfonyl R functionality (CXV) was found to be approximately one-half as active as Aspirin as an analgesic. In comparison to Aspirin, 2-methyl-7-(4-aminobenzene)sulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVII) was two and one-half times more active. The other members of the series, CXIV, CXVI and CXVII also demonstrated good analgetic properties at doses of 64,128 and 128 mg/kg, respectively.

The precise mechanism by which the compounds listed in Table IV exert their analgesic activity has not been

elucidated. Evidence will be presented later in the thesis which favors the hypothesis that compounds CXIV-CXVIII effect their analgesic properties through some form of a narcotic analgesic receptor.

3.5.0.0.0 Pharmacological properties of 1-alkyl-2-substitutedpiperidylidenes.

The good analgesic and antientamoebal properties exhibited by 2-methyl-7-substituted-2,7-diazabicyclo[4.1.0]-hept-3-enes (CXIV-CXVIII) encouraged the further development of other related compounds. It was hoped that these new compounds would also demonstrate some interesting analgesic and antibacterial properties. 1-Methyl-1,2,3,4-tetrahydropyridine (LIII) is a cyclic enamine similar to 1-methyl-1,4-dihydropyridine (XLIII). In accordance, it was hoped that LIII would also undergo 1,3-dipolarcycloaddition with organic azides. It was found that the proposed cycloaddition reactions proceeded in good yield to give 1-methyl-2-substitutedpiperidylidenes. The formation of the piperidylidenes and chemistry of the cycloaddition reaction were discussed earlier.

3.5.1.1.0 Analgesic activity of 1-methyl-2-substituted-piperidylidenes.

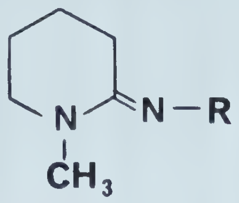
The analgesic activity of 1-methyl-2-substituted-piperidylidenes were determined using the previously

discussed phenylquinone writhing test. The analgesic test results obtained for the 1-methyl-2-substitutedpiperidylidenes are listed as ED_{50} values (Table V). Aspirin, a non-narcotic analgesic, dextropropoxyphene, a weak narcotic analgesic and morphine, a strong narcotic analgesic were included in the study as reference compounds.

1-Methylpiperidylidene-2-methanesulfonamide (CXIX) was found to be a less potent analgesic than Aspirin. The analgesic activity of CXIX was approximately equivalent to the corresponding bicyclic 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]help-3-ene (CXV). The piperidylidene derivative CXXIII having a benzenesulfonyl R substituent exhibited analgesic activity similar to the corresponding 2,7-diazabicyclo[4.1.0]hept-3-ene (CXVI). It is interesting to note that administration of doses greater than or equal to 60 mg/kg sc of CXXIII produced a catatonic state in the mouse. The catatonic state, which lasted from five to fifteen minutes depending upon the drug dosage, was followed by a two hour period of extreme sedation. All of the mice given large doses of CXXIII recovered. The catatonic state produced by CXXIII was unique since none of the other related compounds shown in Table V produced a similar effect. The etiology of the catatonic response observed with CXXIII is unknown.

A large number of 1-methylpiperidylidenes listed in Table V exhibited a greater analgetic activity than

Table V: Analgesic activities of 1-methyl-2-substitutedpiperidylidenes.



Compd	R	Analgesic act.[a] dose (mg/kg sc) at ED_{50}[b]
CXIX	SO_2CH_3	108 ± 4%
CXXI	CN	6.0 ± 5%
CXXIII	SO_2Ph	68 ± 3%
CXXIV	SO_2-C_6H_4-4-CH_3	2.4 ± 3%
CXXV	SO_2-C_6H_4-4-Cl	0.0038 ± 4%
CXXVI	SO_2-C_6H_4-4-OCH_3	0.002 ± 4%
CXXVII	SO_2-C_6H_4-4-NO_2	0.0028 ± 4%
CXXVIII	SO_2-C_6H_4-3-NO_2	0.0028 ± 3%
CXXIX	SO_2-C_6H_4-2-NO_2	0.0018 ± 2%
CXXX	SO_2-C_6H_4-4-$NHCOCH_3$	1.2 ± 3%
CXXXI	SO_2-C_6H_4-4-NH_2	0.007 ± 4%
CXXXIII	SO_2-C_6H_4-3-NH_2	0.0017 ± 6%
CXXXIV	SO_2-C_6H_4-2-NH_2	0.00024 ± 2%
CXXXII	SO_2-3-pyridyl	0.00038 ± 2%
Aspirin TM		50
dextropropoxyphene		56
morphine sulfate		0.038

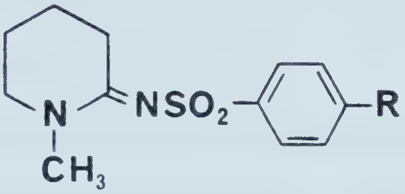
[a] Phenylquinone writhing test. [b] Result is the mean ± SEM of five animals.

morphine sulfate in the phenylquinone writhing test. The two compounds having a 4-chlorobenzenesulfonyl R substituent (CXXV) and a 4-methoxybenzenesulfonyl substituent (CXXVI) were ten and nineteen times more potent, respectively,than morphine sulfate. The most potent analgesic in the 1-methylpiperidylidene series was the 2-aminobenzenesulfonyl derivative (CXXXIV). It exhibited 208,000 times the analgetic activity of Aspirin and one hundred sixty time the potency of morphine sulfate. 1-Methylpiperidylidene-2-(3-pyridyl)-sulfonamide (CXXXII) is also an excellent analgesic having one hundred times the potency of morphine sulfate.

Preliminary structure-activity relationships for the 1-methylpiperidylidenes shown in Table V suggest that an aromatic ring is a required structural component of the R substituent for maximum analgesic activity. Substitution of the phenyl ring by various functionalities was designed to investigate relative potency in relation to hydrophobic (π), electronic (σ) and steric parameters (E_s) of the various substituents. The guidelines used in the evaluation of these parameters was the manual technique[291]. The technique is a non-statistical procedure in which groups of compounds representing various types of ring substitution can be synthesized at one time. The values shown in Table VI illustrate hydrophobic (π) and electronic (σ) values of selected analgesics in relation to those analgesics ED_{50} values in the phenylquinone test. No apparent correlation

exists between analgesic potency of the 1-methylpiperidylidene series and the hydrophobic and electronic parameters. The compounds with the greatest activity (CXXV, CXXVI, CXXVII and CXXXI) show large variations in π, σ and π + σ values yet possess similar analgesic potencies. The analgesic activities of the 4-, 3- and 2-nitro, and 4-, 3- and 2-amino compounds shown in Table V indicate that the 2-phenyl substituted isomer is the most active in each case. The improved analgesic potency of the 2-nitro (CXXIX) and 2-amino (CXXXIV) compounds may be due to an *ortho*-effect.

Table VI: Hydrophobic (π), electronic (σ) and ED_{50} values for selected 1-methylpiperidylidene-2-sulfonamide analgesics.



Compd	R	π	σ	π + σ	ED_{50} (mg/kg sc) on phenylquinone writhing
CXXIII	H	0	0	0	68
CXXIV	CH_3	0.56	-0.17	0.39	2.4
CXXV	Cl	0.71	0.23	0.94	0.0038
CXXVI	OCH_3	-0.02	-0.27	-0.29	0.002
CXXVII	NO_2	-0.28	0.78	0.50	0.0028
CXXX	$NHCOCH_3$	-0.97	0.0	-0.97	1.2
CXXXI	NH_2	-1.23	-0.66	-1.89	0.007

A mild to intense sedation, lasting from thirty minutes to a few hours was generally observed for most 1-methylpiperidylidenes listed in Table V. The effect was dose dependant. It is interesting that CXXIII, which demonstrated unusual catatonic effects at high doses, effected only mild sedation following administration of lower doses. The methanesulfonyl compound (CXIX) elicited neither a sedatory or excitatory response at the dosage levels tested.

The detailed toxicological spectra of the 1-methylpiperidylidenes are unknown. A dose of 120 mg/kg sc of 1-methylpiperidylidene-2-(4-aminobenzene)sulfonamide (CXXXI) administered to five mice caused extreme sedation lasting eight to ten hours. None of the animals died during a subsequent ninety-six hour observation period. These findings suggest that the therapeutic index [lethal dose in 50% of the animals (LD_{50}) divided by effective dose in 50% of animals (ED_{50})] of the 1-methylpiperidylidenes may be very large. A large therapeutic index would imply that the compounds possess a good margin of safety[292].

3.5.1.2.0 The antagonism of 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV) using the narcotic antagonist Naloxone hydrochloride.

Narcotic analgesics elicit antinociceptive responses at low doses by interacting with specific brain opiate

receptors[191-193]. The excellent analgesia exerted by the 1-methylpiperidylidene-2-sulfonamides at low doses suggests the presence of a specific biological receptor responsible for the potent analgesia observed. In this study, the pure narcotic antagonist Naloxone was used to determine whether 1-methylpiperidylidene-2-sulfonamides act at narcotic receptors. Pretreatment of a mouse with a narcotic antagonist would block the antinociceptive properties of analgesics which act specifically at the opiate receptor. Alternatively, the activity of analgesics whose action is independent of the narcotic receptor would not be altered by Naloxone pretreatment. This simple and rapid test was therefore used to illucidate the mechanism of action of the 1-methylpiperidylidene-2-sulfonamides.

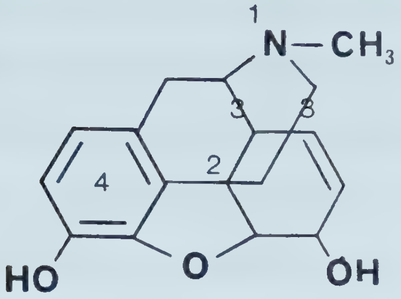
The choice of antinociceptive tests employed with narcotic antagonists is important. The phenylquinone writhing test[290] has been considered useful for testing narcotic agonists and antagonists[261] and was utilized in our experiments. 1-Methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV) administered at a dose of 5 mg/kg sc using the phenylquinone writhing test completely inhibited the writhing response in the mouse (100% inhibition). Pretreatment of the mice using a 1 mg/kg sc dose of the narcotic antagonist Naloxone hydrochloride followed by injection of CXXV at 5 mg/kg sc resulted in a 45% inhibition of phenylbenzoquinone induced writhing. These results indicate that

Naloxone hydrochloride partially blocks the analgesic effect of CXXV. Increasing the pretreatment dose of Naloxone hydrochloride to 5 mg/kg sc while administering the same dose of CXXV further reduced inhibition to 30%. Although a complete blockage of the analgesic effects of CXXV was not obtained, these results do imply that the 1-methylpiperidylidene-2-sulfonamides may elicit their analgesic responses at a narcotic opiate receptor.

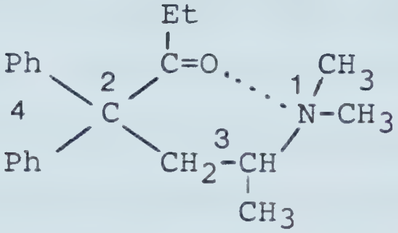
3.5.1.3.0 Structural features common to narcotic analgesics and their relationship to 1-methylpiperidylidene-2-sulfonamides.

A number of structural features common to narcotic analgesics have been discussed in detail in the introduction of this thesis[160]. The present discussion will focus on these necessary structural features as they relate to a number of "typical" narcotic analgesics and to the 1-methylpiperidylidene-2-sulfonamides. Figures 1 outlines the general features common to good narcotic analgesics. This figure also indicates the structure of four highly active analgesics, viz: morphine (XV), methadone (LXIII), meperidine (XVI) and the 1-methylpiperidylidene-2-sulfonamides (CLXXV). The tertiary amino group present in morphine, methadone and meperidine is designated by the number 1 in each structure. The narcotic analgesics shown all possess at least one small substituent on the nitrogen atom. The

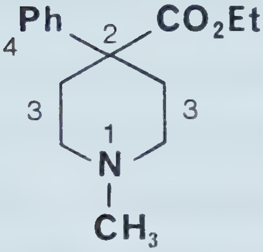
Figure 1: Structural features common to narcotic analgesics.



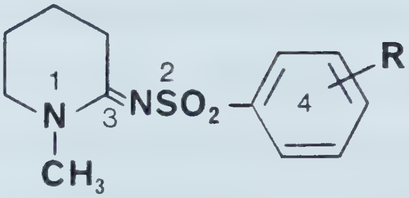
Morphine (XV)



Methadone (LXIII)



Meperidine (XVI)

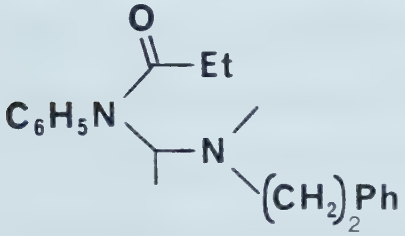


1-Methylpiperidylidenes (CLXXV)

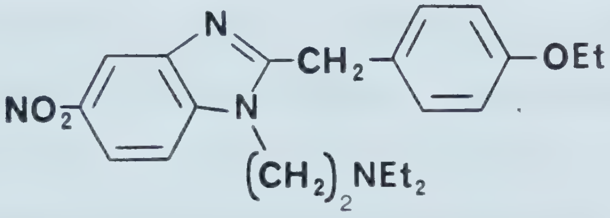
1. A 3° amino group, the group on nitrogen being small.
2. A central carbon atom of which none of the valences are hydrogen.
3. A two carbon chain separating the 3°-N and central carbon atoms.
4. A phenyl group attached directly to the central carbon atom.

1-methylpiperidylidene-2-sulfonamides (CLXXV) also have a tertiary amino group with a small alkyl substituent. In addition, the structure of CLXXV includes a piperidine ring system typical of narcotic analgesics. The central carbon atom, labelled number 2, is easily discernible in morphine, methadone and meperidine. 1-Methylpiperidylidene-2-sulfonamides do not possess a central carbon atom. In the case of CLXXV, the sulfur atom of the sulfonyl group likely serves the function of the central carbon atom. The structure CLXXV also does not contain a two carbon chain between the tertiary amino and central carbon atoms (number 3). The two carbon chain is visible in morphine, methadone and meperidine. Comparisons of Dreiding molecular structures of morphine (XV) and 1-methylpiperidylidene-2-sulfonamides (CLXXV) indicate that the interspatial distances between the tertiary amino and central carbon atoms of XV are very close to those of the tertiary amino and central sulfur atoms of CLXXV. Therefore, the imine group in 1-methylpiperidylidene-2-sulfonamides is comparable to the two carbon chain found in most narcotic analgesics. The presence of a phenyl group in each structure is indicated by number 4. In CLXXV the phenyl substituent is attached directly to the central "sulfur" atom. Compounds which possess structural features comparable to those discussed above are prerequisite components of any effective narcotic analgesic.

The examination of the four important structural features characteristic of narcotic analgesics indicates that the 1-methylpiperidylidene-2-sulfonamides are actually closely related from a structural viewpoint to analgesics such as morphine. Both morphine and CLXXV contain tertiary amino groups and aromatic rings. The piperidylidene CLXXV is an example of a narcotic analgesic which contains a central sulfur atom rather than a central carbon atom. A few narcotic analgesics which incorporate a tertiary nitrogen in place of a central carbon atom have been investigated. Diampromide and Etonitazene are very potent analgesics which also show high addiction liabilities[285].



Diampromide

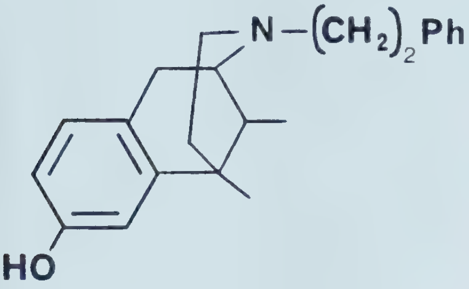


Etonitazene

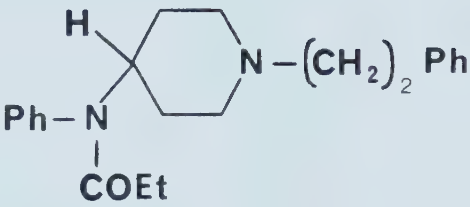
3.5.2.0.0 1-Arylalkylpiperidylidene-2-sulfonamides with narcotic agonist properties.

Substitution of the N-methyl group in narcotic analgesics by N-phenylethyl or N-(4-aminophenyl)ethyl functionalities generally imparts a three to ten fold increase in analgetic activity[285]. Phenazocine (LXVI), for example, is a clinically useful analgesic which incorporates

a N-phenylethyl substituent. Fentanyl (XVII), a very potent member of the meperidine analgesic family, also contains a N-phenylethyl group.



LXVI

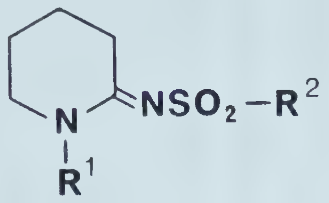


XVII

In an attempt to produce more potent analgesics within the piperidylidene series, substitution of an arylalkyl moiety for the N-methyl group in 1-methylpiperidylidene-2-sulfonamides (CLXXV) was performed. Reaction of 4-chlorobenzenesulfonyl azide with 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) afforded 1-(2-phenylethyl)-piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII) in 25% yield. Subsequent nitration of CXXXVII and reduction of the resulting nitro group afforded 1-[2-(4-nitrophenyl)-ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXL) in 61% yield and 1-[2-(4-aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXLI) in 67% yield, respectively.

These arylalkyl compounds exhibited excellent analgesia in the phenylquinone writhing test (Table VII). The N-phenylethyl derivative CXXXVII displayed only one-half the analgesic activity of the corresponding N-methyl

Table VII: Analgesic activity of 1-arylalkylpiperidylidene-2-sulfonamides.



Compd	R^1	R^2	analgesic act., inhib act. on phenylquinone writhing[a]	
			dose (mg/kg sc)	% inhib
CXXXVII	CH_2CH_2Ph	C_6H_4-4-Cl	0.007	50 ± 3
CXXXVIII	CH_2CH_2Ph	C_6H_4-4-NH_2	0.20	56^b ± 2
CXXXIX	CH_2CH_2Ph	3-pyridyl	0.20	65^b ± 4
CXL	$CH_2CH_2C_6H_4$-4-NO_2	C_6H_4-4-Cl	0.0000037	50 ± 5
CXLI	$CH_2CH_2C_6H_4$-4-NH_2	C_6H_4-4-Cl	0.000034	50 ± 3
CXXV	CH_3	C_6H_4-4-Cl	0.0038	50 ± 4
morphine sulfate			0.038	50

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[a] The result is the mean value or ED_{50} value ± SEM for five animals. [b] Analgesic activity tested with a single dose.

compound CXXV. This reduction in analgesic potency is interesting since most N-phenylethyl narcotic analgesics are more potent than their N-methyl counterparts. Substitution of nitro or amino in the arylalkyl ring, as noted in CXL and CXLI, resulted in pronounced increases in analgesic potency. The 4-aminophenylethyl compound CXLI and the 4-nitrophenylethyl derivative CXL were, 1100 and 10,200 times more potent respectively than morphine sulfate. Results from the phenylquinone writhing test suggest that these two compounds may be among the most potent analgesics known. It can be estimated using the results obtained in laboratory mice, that as little as 0.1 mg of CXL would achieve an equivalent ED_{50} in a seventy-five kg person assuming that a man requires approximately ten times the amount of CXL that a mouse requires[310].

3.5.3.0.0 1-Alkylpiperidylidene-2-sulfonamides possessing partial agonist properties.

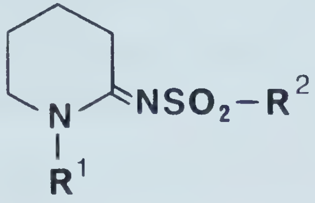
Replacement of the N-methyl group present in narcotic analgesics by larger N-alkyl functionalities results in a reduction or complete loss of analgesic activity[153,285]. The pharmacological consequence of incorporating larger N-alkyl substituents results in an increase in analgesic antagonistic activity. Recently, partial agonists have been used in clinical practice as narcotic analgesics. The partial agonists, exemplified by nalbuphine (LXXI),

butorphanol (LXXII) and buprenorphine (LXXIII-c), exhibit good analgesic properties with minimal untoward side-effects. Some typical substituents attached to the nitrogen atom of partial agonists include cyclopropylmethyl, cyclobutylmethyl, cyclopentyl and allyl groups.

The replacement of the N-methyl group present in 1-methlpiperidylidene-2-sulfonamides (CLXXV) with a phenylethyl or substituted phenylethyl moiety produced highly potent analgesic compounds. It would be expected that larger alkyl groups replacing the methyl substituent on nitrogen in CLXXV would similarily provide compounds possessing narcotic analgesic antagonist or partial-agonist activities.

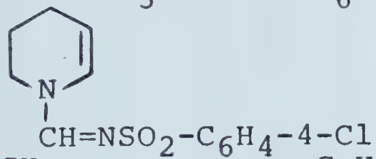
The reaction of appropriate 1-alkyl-1,2,3,4-tetrahydropyridine and organic sulfonyl azides now provides a series of 1-alkylpiperidylidene analgesic compounds. The analgesic agonist activities of the 1-alkylpiperidylidene-2-sulfonamides are summarized in Table VIII. Three azides having different physicochemical properties were selected for the preparation of the compounds illustrated in Table VIII to afford R^2 substituents with a variety of electronic, lipophilic and steric features. It was found that piperidylidenes containing the same R^1 group and various R^2 substituents possessed very similiar analgesic properties. The 3-pyridyl R^2 substituent conferred slightly better analgesic activity than other groups. The nature

Table VIII: Analgesic activity of 1-cycloalkylmethyl(*n*-propyl,isobutyl)piperidylidene-2-sulfonamides.



Compd	R^1	R^2	analgesic act., inhib act. on phenylquinone writhing[a] dose (mg/kg sc)	 % inhib
CIL	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	$C_6H_4\text{-}4\text{-}Cl$	2.3	50 ± 8
CL	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	$C_6H_4\text{-}4\text{-}NH_2$	2.0	49^b ± 9
CLI	$CH_2\text{-}\underline{c}\text{-}C_3H_5$	3-pyridyl	2.0	50^b ± 3
CLII	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	$C_6H_4\text{-}4\text{-}Cl$	0.01	50 ± 4
CLIII	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	$C_6H_4\text{-}4\text{-}NH_2$	0.2	61^b ± 3
CLIV	$CH_2\text{-}\underline{c}\text{-}C_4H_7$	3-pyridyl	0.2	69^b ± 3
CLIX	$CH_2CH_2CH_3$	$C_6H_4\text{-}4\text{-}Cl$	1.4	50 ± 4
CLX	$CH_2CH_2CH_3$	$C_6H_4\text{-}4\text{-}NH_2$	2.0	59^b ± 3
CLXI	$CH_2CH_2CH_3$	3-pyridyl	2.0	82^b ± 2
CLXII	$CH_2CH(CH_3)_2$	$C_6H_4\text{-}4\text{-}Cl$	2.0	50 ± 4
CLXIII	$CH_2CH(CH_3)_2$	$C_6H_4\text{-}4\text{-}NH_2$	2.0	59^b ± 2

Table VIII: Continued;

Compd	R^1	R^2	analgesic act., inhib act. on phenylquinone writhing[a] dose (mg/kg sc)	% inhib
CLXIV	$CH_2CH(CH_3)_2$	3-pyridyl	2.0	$65^b \pm 3$
CLXXIII	$CH=CHCH_3$ (E)	C_6H_4-4-Cl	0.013	50 ± 5
CLXXIV			2.0	$41^b \pm 6$
CXXV	CH_3	C_6H_4-4-Cl	0.0038	50 ± 4
morphine sulfate			0.038	50

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[a] The result is the mean value or ED_{50} ± SEM for five animals. [b] Analgesic activity tested with a single dose.

of the piperidylidene R^2 functionality apparently has little effect on the analgesic potency.

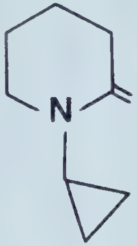
All of the compounds listed in Table VIII possessed weaker analgesic properties than the corresponding N-methyl derivatives represented by 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV). The compounds CLII through CLIV inclusive, all of which have a R^1 cyclobutylmethyl group, possessed good analgesic activity. The 4-chlorophenyl derivative CLII had approximately four times the analgesic potency of morphine sulfate and two-fifths the potency of 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV). Good analgesic activity was also demonstrated by the E-1-(1-propenyl) derivative CLXXIII. The ED_{50} for CLXXIII corresponds to an analgesic potency similar to that for CLII. The other 1-alkylpiperidylidene-2-sulfonamides listed in Table VIII exhibited considerably weaker analgesic activities than those of morphine sulfate and CXXV. The structurally novel tetrahydropyridine CLXXIV also possessed mild pain killing properties.

The analgesics listed in Table VIII also possessed narcotic antagonistic properties which were determined using the phenylquinone writhing test. Antagonistic activity was demonstrated toward morphine sulfate and 1-methylpiperidylidene-2-(4-chlorophenylsulfonamide) (CXXV). Some results are illustrated for the partial agonist 1-cyclopropylmethyl-

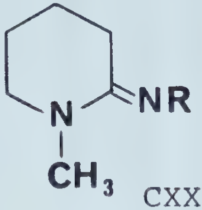
piperidylidene-2-(4-chlorophenyl)sulfonamide (CIL) (Table IX). A 2.0 mg/kg sc dose of the piperidylidene agonist-antagonist analgesic (CIL) almost completely inhibited the analgesic effect of morphine sulfate (0.2 mg/kg sc). A 10 mg/kg sc dose of CIL [experiment (2)] was required for complete inhibition. The piperidylidene CIL also inhibited the analgesic effect of 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV). A partial analgesic block of CXXV (2.0 mg/kg sc) was obtained using a 0.5 mg/kg sc dose of CIL [experiment (3)] while a full blockage was attained using a 2.0 mg/kg sc dose of CIL [experiment (4)]. It may be concluded from these results that 1-cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide is a partial agonist-antagonist narcotic analgesic.

The other analgesics listed in Table VIII also behaved as partial agonist-antagonists. Antagonistic properties similar to CIL against 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV) and morphine sulfate were exhibited by 1-n-propylpiperidylidene-2-(4-chlorophenyl)-sulfonamide (CLIX). 1-Isobutylpiperidylidene-4-(2-chlorophenyl)sulfonamide (CLXII) displayed slightly better antagonistic qualities than the corresponding 1-cyclopropylmethyl compound CIL. A 0.5 mg/kg sc dose of CLXII gave a near complete antagonism of the analgesic effects of CXXV while a 2.0 mg/kg sc dose of CIL was required to induce a similar blockade of CXXV. The 1-isobutylpiperidylidene CLXII showed

Table IX: Analgesic agonist-antagonist results for 1-cyclopropylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CIL) using the phenylquinone writhing test.



CIL



CXXV

R = SO_2-C_6H_4-4-Cl

MS = morphine sulfate

A. CONTROLS

Dose (mg/kg sc)	CIL (% Inhib)[a]	CXXV (% Inhib)[a]	MS (% Inhib)[a]
0.2	nt	nt	80 ± 4
0.5	36 ± 5	nt	nt
2.0	45 ± 3	93 ± 2	nt
5.0	nt	100 ± 0	nt
10.0	69 ± 2	nt	nt

B. ANTAGONIST ACTIVITIES

Expt	Antagonist dose (CIL) (mg/kg sc)	agonist dose (mg/kg sc)	% Inhib[a] (Result)
(1)	2.0	MS - 0.2	55 ± 3 (Near complete block)
(2)	10	MS - 0.2	66 ± 3 (Complete block)
(3)	0.5	CXXV - 2.0	53 ± 4 (Partial block)
(4)	2.0	CXXV - 2.0	49 ± 6 (Complete block)

---

[a] The result is the mean ± SEM for five animals. [b] nt, not tested

antagonistic properties toward morphine sulfate comparable to that of the 1-cyclopropylmethyl compound CIL. A 0.5 mg/kg sc dose of 1-cyclobutylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CLII) fully inhibited analgesia produced by CXXV. In addition, CLII (0.5 mg/kg sc) also completely inhibited the analgesic effect caused by a 2.0 mg/kg sc dose of 1-(2-phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII). Antagonistic properties similar to those of CLII were observed for E-1-(1-propenyl)-piperidylidene-2-(4-chlorophenyl)sulfonamide (CLXXIII). The 1,2,3,4-tetrahydropyridine compound (CLXXIV) possessed no analgesic antagonist properties. The agonist-antagonist activities for all compounds listed in Table VIII were not determined. 1-Alkylpiperidylidene-2-sulfonamides having 4-aminophenyl or 3-pyridyl R^2 groups however would be expected to closely resemble the responses of compounds with 4-chlorophenyl R^2 groups which were discussed in detail earlier.

3.5.4.0.0 Receptor sites for 1-substitutedpiperidylidene-2-sulfonamides.

The experiments discussed previously indicate that 1-substitutedpiperidylidene-2-sulfonamides are analgesics which interact with a narcotic receptor. The narcotic antagonist Naloxone (1 mg/kg sc) partially blocks the analgetic effects of 1-methylpiperidylidene-2-sulfonamide (CXXV)

(5 mg/kg sc). Replacement of the N-methyl substituent present in CXXV by a N-arylalkyl moiety as demonstrated by 1-[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)-sulfonamide (CXL) provides a highly potent analgesic. A N-arylalkyl group is an important structural component of narcotic analgesics present in fentanyl and phenazocine. The 1-cycloalkylmethyl(n-propyl, isobutyl)piperidylidene-2-sulfonamides prepared are partial-agonist analgesics. Antagonistic activity was demonstrated toward morphine sulfate, CXXV and 1-(2-phenylethyl)-piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII).

In order to qualitatively determine whether 1-methylpiperidylidene- and 1-alkyl(cycloalkyl)piperidylidene-2-sulfonamides interact with brain receptor sites, brain receptor binding experiments using radiolabelled narcotic analgesics would have to be executed. A basic conception of the type of narcotic receptor involved in piperidylidene analgesics, can however be gained by using antinociception tests other than the phenylquinone writhing experiment and appropriate antagonist blocking experiments. The following discussion will focus on these experiments and attempt to classify the piperidylidene analgesics by narcotic receptor type.

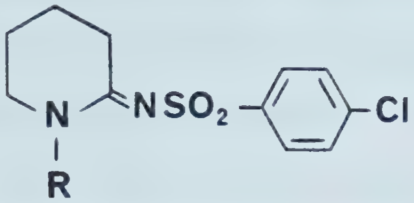
Tyers[260] has determined that μ-agonists are effective analgesics in the writhing and hot-plate tests.

The κ-agonists are active in the writhing test and less effective in heat stimulus tests. The σ-analgesics are inactive in both tests.

Antinociception results for 1-methyl(cyclopropylmethyl)piperidylidene-2-(4-chlorophenyl)sulfonamides using the hot-plate test[293,294] are presented in Table X. Good analgesia was demonstrated for 1-methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV) in the phenylquinone and hot-plate experiments. These results imply that CXXV acts at a narcotic μ-receptor. The ED_{50} for 1-cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CIL) using the hot-plate test could not be determined due to lack of solubility in isotonic saline, the injection vehicle. It is likely, however, that CIL is less active in the hot-plate experiment and thus acts on the κ-receptor. Most typical partial agonists, such as butorphanol and nalbuphine, are agonists at the κ-receptor and antagonists at the μ-receptor.

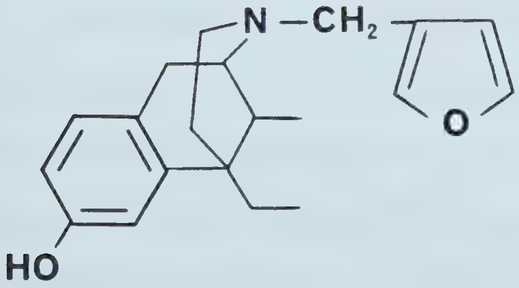
An interesting experimental narcotic antagonist, MR-2266, has recently been discovered. This antagonist is only active against analgesic agonists whose activity is demonstrated at the κ-receptor. For example, bremazocine, a κ-agonist analgesic is largely unaffected by Naloxone yet its analgesia is completely blocked by MR-2266[197].

Table X: Analgesic data for some piperidylidene analgesics.



Compd	R	Phenylquinone writ. ED$_{50}$(mg/kg sc)[a]	Hot plate ED$_{50}$(mg/kg sc)[a]
CXXV	CH_3	0.0038 ± 4%	1.6 ± 2%
CIL	CH_2-c-C_3H_5	2.3 ± 8%	200
morphine sulfate		0.038	3.1

[a] The result is the mean value ± SEM for five animals.



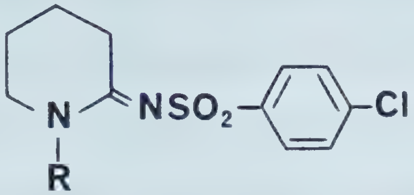
MR-2266

The analgesic results obtained following pretreatment with MR-2266 hydrochloride (MR-2266 HCl) before dosing with CXXV and CIL in the phenylquinone writhing test are shown in Table XI. The data indicates that MR-2266 HCl does

not significantly block μ-agonist morphine sulfate induced analgesia and only slightly antagonizes the analgesia of CXXV. 1-Methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV) is approximately equipotent with morphine sulfate in the hot-plate test, is inhibited by 1-cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CIL) and only partially inhibited by MR-2266 HCl. It is likely from the analgesic and analgesic blocking experiments discussed previously that CXXV and similar 1-methylpiperidylidenes are narcotic μ-agonists. Incomplete antagonism of CXXV by Naloxone make this conclusion only speculative in nature. Pretreatment of mice with MR-2266 HCl before CIL dosing results in essentially a complete inhibition of analgesia. It is very likely therefore, that CIL and similar piperidylidene partial agonists are analgesics at the κ-receptor.

The results presented in this portion of the thesis have shown that 1-substitutedpiperidylidene-2-sulfonamides and possibly the 2-methyl-7-substituted-2,7-diazabicyclo-[4.1.0]hept-3-enes (Table IV) are analgesics which interact with an opiate receptor. Closer examination of important structural features of typical narcotic agonists and 1-methylpiperidylidene-2-sulfonamides pointed out many similar structural components. Preliminary experiments indicate that 1-methylpiperidylidene-2-sulfonamides are agonists at the μ-receptor and 1-cycloalkylmethyl(n-propyl, isobutyl)-

Table XI: Antagonism of selected piperidylidene analgesics with MR-2266 HCl in the phenylquinone writhing test.



Compd	R	Normal % inhib at 2 mg/kg sc	% Inhib at 2 mg/kg sc after MR-2266 HCl (1 mg/kg sc)
CXXV	CH_3	93 ± 2	74 ± 4
CIL	$CH_2\text{-}\underline{c}\text{-}CH_3$	45 ± 3	9 ± 4
morphine sulfate		88 ± 3	82 ± 3

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[a] The result is the mean value ± SEM for five animals.

piperidylidene-2-sulfonamides agonists at the κ-receptor.

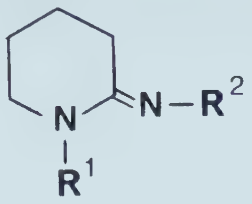
3.5.5.0.0 Antimicrobial activity of 1-methyl(cyclopropylmethyl)piperidylidene-2-cyan(sulfon)amides.

The antimicrobial activities of the 1-methyl(cyclopropylmethyl)piperidylidene-2-cyan(sulfon)amides prepared were determined against a variety of gram positive and gram negative microrganisms. The detailed procedure employed in the antimicrobial screen is described in the experimental portion of this thesis. The 1-methyl(cyclopropylmethyl)-

piperidylidenes were dissolved in methanol at various concentrations and impregnated onto 4 mm paper discs. Antibiotic agar plates were prepared using 1 mL of overnight bacterial culture in 200 mL of media. The bacterial suspension was poured into 20 x 20 cm forms and the discs were placed on the surface after the media solidified. The zones of inhibition surrounding the discs were measured following overnight incubation at 37°C. The amount of inhibition was compared to zones obtained with known concentrations of standard antibiotics.

The antimicrobial results for 1-methyl(cyclopropylmethyl)piperidylidene-2-cyan(sulfon)amides are summarized in Table XII. Very little antimicrobial activity was associated with the 1-methyl(cyclopropylmethyl)piperidylidene-2-cyan(sulfon)amides. 1-Methylpiperidylidene-2-(4-nitrophenyl)sulfonamide (CXXVII) and 1-cyclopropylmethylpiperidylidene-2(4-chlorophenyl)sulfonamide (CIL) showed slight activity against _S_. _dysenteria_ and _M_. _flavis_, respectively. The poor antimicrobial activities observed for the test compounds listed in Table XII prompted us to discontinue testing of these compounds as potential antibacterial agents.

Table XII: Antimicrobial zones of inhibition of 1-methyl(cyclopropylmethyl)piperidylidene-2-cyan(sulfon)amides versus various bacteria.



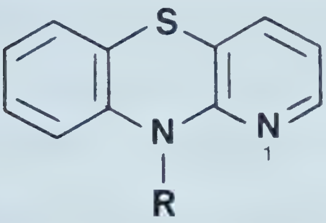
				Zones of inhib(mm)[c] against[d]:		
Compd[a,b]	R^1	R^2	Conc(μg)	*S. dysenteria*[e]	*M. flavis*[f]	*S. typhi*[g]
CCXXVI	CH_3	$SO_2-C_6H_4-4-OMe$	200	-	-	tr
CXXVII	CH_3	$SO_2-C_6H_4-4-NO_2$	200	- 10	-	-
CIL	$CH_2-\underline{c}-C_3H_5$	$SO_2-C_6H_4-4-Cl$	200	-	- 10	-
			50	-	- 8	-
neomycin (30 μg)				- 12	16	13
tetracycline (30 μg)				- 28	- 32	- 33
chloramphenicol (30 μg)				- 25	- 28	14
penicillin G (10 μg)				- 30	30	8
streptomycin (10 μg)				14	0	14
vancomycin (30 μg)				- 18	20	13

---

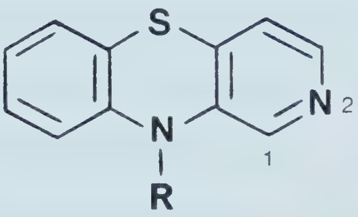
[a] The compounds CXIX(R^1=CH_3,R^2=SO_2CH_3), CXXI(R^1=CH_3,R^2=CN), CXXIII(R^1=$CH_3$$R^2$=$SO_2Ph$), CXXIV($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-4-CH_3$), CXXV($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-4-Cl$),CXXVIII($R^1$=$CH_3$,R=$SO_2-C_6H_4-3-NO_2$) CXXIX($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-2-NO_2$), CXXX($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-4-NHCOCH_3$),CXXXI ($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-4-NH_2$), CXXXIII($R^1$=$CH_3$,$R^2$=$SO_2-C_6H_4-3-NH_2$), CXXXII($R^1$=$CH_3$,$R^2$=3-pyridyl), CL($R^1$=$CH_2-\underline{c}-C_3H_5$,$R^2$=$SO_2-C_6H_4-4-NH_2$), CLI($R^1$=$CH_2-\underline{c}-C_3H_5$,$R^2$=$SO_2$-3-pyridyl) were inactive against all bacterial strains at 200,50 and 10 μg. [b] Compounds CXXVI,CXXVII andCIL were inactive against bacteria listed in [d]. [c] For interpretation, a minus sign indicates partial activity, tr indicates a trace of inhibition. [d] Other bacteria tested include *Streptococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Psuedomonas aeruginosa*, *Proteus morganii* and *Staphylococcus aureus*. [e] *Shigella* strain. [f] *Micrococcus* strain. [g] *Salmonella* strain.

3.6.0.0.0 Structure-Activity relationships for azaphenothiazines.

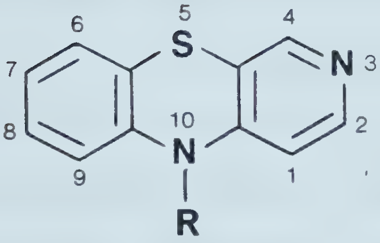
Analogs of phenothiazine in which an annular ring nitrogen is part of the ring structure are known as pyridobenzothiazines (azaphenothiazines). The four known isomeric azaphenothiazines are illustrated below.



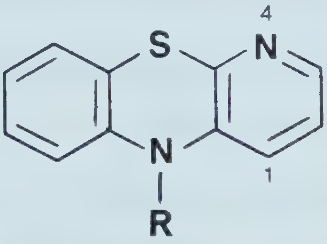
CXI



C



CLXXVI

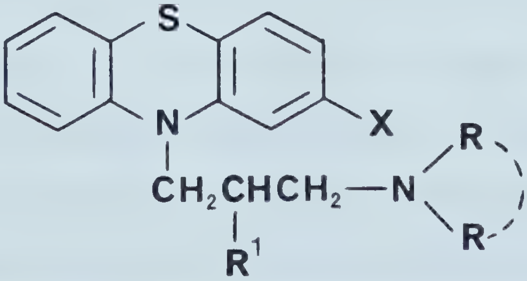


CLXXVII

10H-Pyrido[3,2-b][1,4]benzothiazines(1-azaphenothiazines, CXI), 10H-Pyrido[4,3-b][1,4]benzothiazines(2-azaphenothiazines, C), 10H-Pyrido[3,4-b][1,4]benzothiazines(3-azaphenothiazines, CLXXVI), and 10H-Pyrido[2,3-b][1,4]benzothiazines (4-azaphenothiazines, CLXXVII).

A number of 1-azaphenothiazine derivatives have useful antihistaminic, antiemetic and antitussive properties. Clinically important 1-azaphenothiazines include prothipendyl (CXI-a,R=$(CH_2)_3N(CH_3)_2$), isothipendyl (CXI-b,R=$CH_2CH(CH_3)N(CH_3)_2$), pervetral (CXI-c,R=$(CH_2)_3$-N N-$(CH_2)_2OH$) and pipazethate (CXI-d,R=$CO_2(CH_2)O(CH_2)$-N). The pharmacology of these compounds has been highlighted in the introduction of this thesis and reviewed in detail elsewhere[266]. Isomeric 2-aza (C), 3-aza (CLXXVI) and 4-azaphenothiazines (CLXXVII) having R groups similar to the clinically useful 1-azaphenothiazine (CXIa-d) do not exhibit the same degree or variety of pharmacological properties.

The wide spectrum of pharmacological properties observed for the phenothiazine series (CLXXVIII)[295,296] stimulated interest into the study of azaphenothiazine derivatives possessing similar N-10 substituents. A number of structural modifications at the N-10 position of phenothiazines have been correlated with pharmacological activity.



CLXXVIII

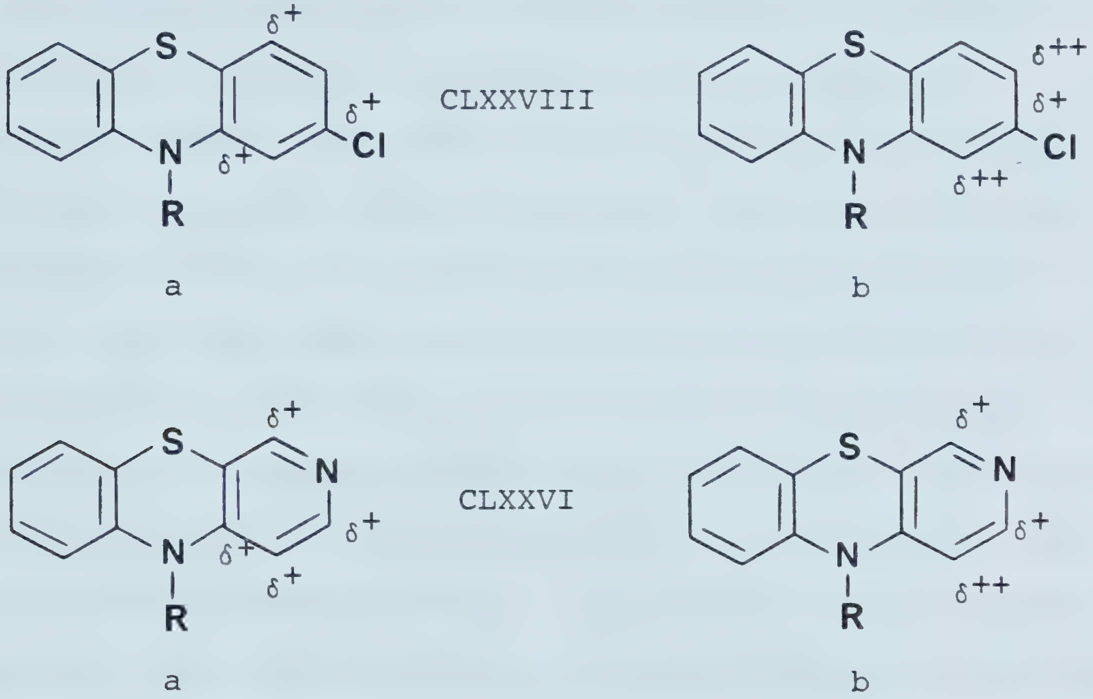
Antipsychotic activity is optimal when the basic amino centre and N-10 nitrogen are separated by three carbon

atoms. Compounds with a two carbon chain possess only mild tranquilizing activity but have marked antihistaminic and antiparkinsonism effects. These effects are further enhanced by branching of the chain at the R^1 position. Small groups such as methyl R^1-substituents enhance antihistaminic and antipruritic properties while reducing tranquilizing activity. This effect may arise as a result of decreased coplanarity of the benzene rings when the R^1-methyl and 1,9-peri hydrogens on the phenothiazine ring undergo steric repulsion. Neuroleptic potency is often decreased as the size of the N-alkyl substituent increases. A significant enhancement of activity however is often observed when a piperazine ring replaces the terminal dimethylamino moiety. A complete loss of central effects results from quaternization of the side chain nitrogen. This is due to a decrease in lipid solubility and a decreased penetration of the CNS.

Examination of the resonance and inductive effects for 2-chlorophenothiazines (CLXXVIII) and 3-azaphenothiazines (CLXXVI) is illustrated by Figure 2. The resonance effects in CLXXVIII-a and CLXXVI-a display similar charge distribution effects. These structures indicate that the C-2, C-4 and C-1a are electron deficient in both the phenothiazine CLXXVIII and 3-azaphenothiazine CLXXVI. The inductive effect of the 2-chloro substituent in CLXXVIII-b is

strongest at the C-2 carbon atom and falls off rapidly with distance from this centre. The inductive effect of the pyridyl nitrogen in CLXXVI-b is expected to be most pronounced at the ortho-positions and will decrease with increasing distance from the nitrogen. The C-2 position is most electron deficient due to the inductive effect of Cl and N in CLXXVIII-a and CLXXVI-b respectively.

Figure 2: Summary of Resonance and Inductive effects for 2-chlorophenothiazine (CLXXVIII) and 3-azaphenothiazine(CLXXVI).



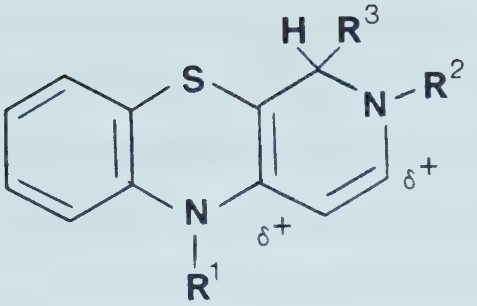
Resonance Effects

Inductive Effects

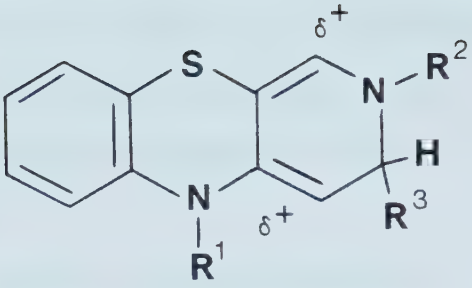
3-Azaphenothiazines possessing a partially reduced pyridyl ring such as CLXXIX and CLXXX will likely exhibit activity similar to phenothiazines having an electron-withdrawing group at C-2 *viz*: A benzene ring bearing a -I sub-

stituent such as chloro or nitro has charge distributions similar to the π-electron deficient 1,2-dihydropyridines. A number of nmr studies have shown that the charge distribution of 1,2-dihydropyridines is similar to that of pyridine and nitrobenzene[271,272]. The chemical shifts for 1,2-dihydropyridine protons (CLXXVI) listed in order of increasing δ value are $H_6>H_4>H_3>H_5$. This indicates that the lowest π-electron density is at C-6 and C-4 while C-3 and C-5 possess higher π-electron densities. It would be expected that the reduced pyridyl 3-azaphenothiazines CLXXIX and CLXXX would have similar electron densities to the reduced 1,2-dihydropyridine CLXXXI. It is important to note that the electron distribution of CLXXIX is similar to that observed with 2-chlorophenothiazine (CLXXVIII-a) and 3-azaphenothiazine (CLXXVI-a). The nature of the R^3 group present in the dihydropyridyl-3-azaphenothiazines CLXXIX and CLXXX significantly influences charge distribution. A R^3 phenyl substituent would decrease the electron density on the centre bearing the R^3 group. An increase in electron density would be observed if R^3 were methyl or n-butyl.

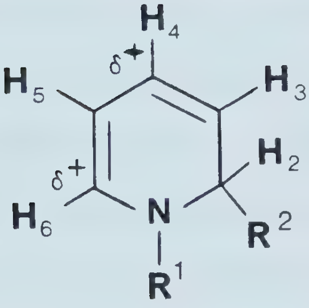
Dreiding molecular models show that 2-chlorophenothiazine (CLXXVIII) and 3-azaphenothiazine (CLXXVI) have quite similar puckered or "V-shaped" skeletal backbones, with the axis being about the sulfur - N-10 plane. Dreiding models also indicate that dihydropyridyl-3-azaphenothiazines (CLXXIX and CLXXX) have similar structural conformations to



CLXXIX



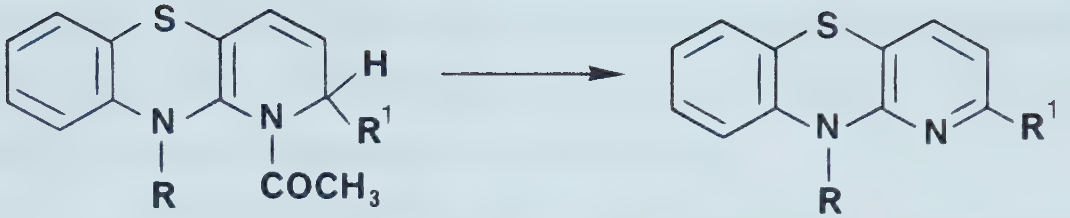
CLXXX



CLXXXI

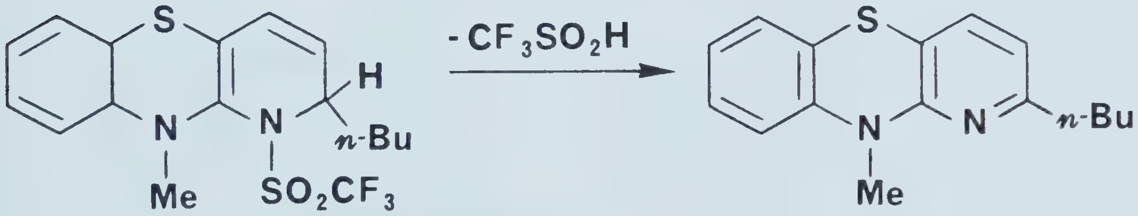
CLXXVIII and CLXXVI. The N-3 nitrogen in CLXXIX is the only atom whose conformation varies significantly from the equivalent N-3 nitrogen in CLXXVI or C-3 carbon in CLXXVIII. It is likely therefore that the neuroleptic receptor site which accommodates 2-chlorophenothiazine (CLXXVIII) would also accommodate CLXXIX and CLXXXI.

A study was initiated to prepare 3-azaphenothiazines possessing a partially reduced pyridyl ring which should have pharmacological activities similar in nature to phenothiazines bearing a C-2 electron-withdrawing functionality. The 3-azaphenothiazines CLXXVI have been less extensively investigated than their 1-aza-isomer CXI. Their inductive and resonance effects however are similar to the 2-chlorophenothiazines CLXXVIII (Figure 2). Therefore the 3-azaphenothiazine system should be of pharmacological importance as neuroleptics, antihistaminics and antiepileptics. Furthermore, if the partially reduced 3-azaphenothiazines do not exhibit pharmacological activity due to the parent structure they may act as pro-drugs. Precedence for this postulate is borne out by the observation that 1-methyl-1,6-dihydropyridine-2-carbaldoxime(pro-2 PAM)(XI) is an efficient pro-drug of N-methylpyridinium-2-carbaldoxime chloride (IX)[61-63]. Studies in the 1-azaphenothiazine system adds further credence to the use of 3-azaphenothiazines as pro-drugs. Knaus and Pasutto[297] suggest that some N-acetyl-1,2-dihydropyridines (CLXXXII) may under-



CLXXXII CLXXXIII

go aromatization to give the corresponding aromatic compound CLXXXIII. The facile elimination of CF_3SO_2H from the dihydro-1-azaphenothiazine CLXXXIV affords CLXXXV[272].



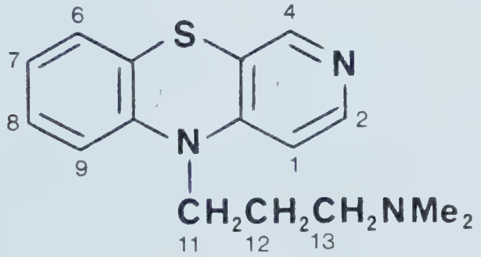
CLXXXIV CLXXXV

3.7.1.0.0 N[10]-Alkylation of 10H-pyrido[3,4-b][1,4]-benzothiazine (CLXXVI).

The alkylation of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with dialkylaminoalkyl chlorides was effected using the procedure of Clarke and coworkers[270]. Addition of 3-dimethylaminopropyl chloride to a suspension of CLXXVI and sodium hydride in toluene and dioxane (4:1) afforded 10-(3-dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]-benzothiazine (CXII)[270] in 87% yield. The preparation

of other 10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazines was accomplished in a similar manner. The synthetic data are presented in Table XIII.

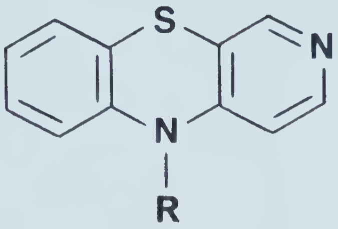
The nmr spectrum(δ) of CXII exhibits a 2H triplet ($J_{11,12}$=7Hz) of triplets ($J_{12,13}$=7Hz) at 1.84 due to the C_{12}-H, a 6H singlet at 2.2 attributed to the methyl, a 2H triplet ($J_{12,13}$=7Hz) at 2.4 due to the C_{13}-H, a 2H triplet ($J_{11,12}$=7Hz) ascribed to the C_{11}-H, a 1H doublet ($J_{1,2}$=6Hz) at 6.69 attributed to the C_1-H, a 4H multiplet at 7.0 due to the C_6-C_9-H, a 1H singlet at 8.13 assigned to the C_4-H, and a 1H doublet ($J_{1,2}$=6Hz) at 8.22 due to the C_2-H.

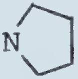
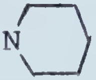
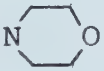


CXII

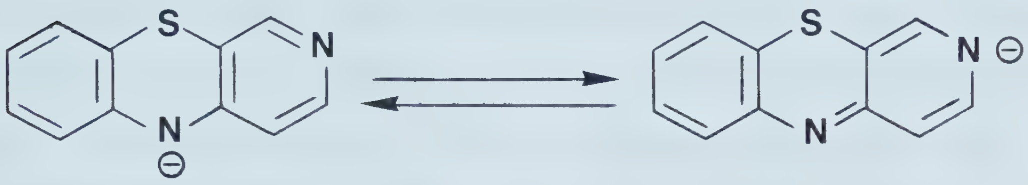
Addition of sodium hydride to 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI) in toluene and dioxane, and heating at reflux results in abstraction of the N^{10}-proton from CLXXVI. The resulting N^{10}-anion is in resonance stabilization with the N^3-anionic species as shown below. Addition of an alkylating agent to CLXXVI and sodium hydride generally results in addition at the N^{10}-position. The N^{10}-position is the favored alkylation site for CLXXVI

Table XIII: Synthetic data for 10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazines.



Compd	R	Reaction time (h)	% yield	mp(°C)
CXII	$(CH_2)_3N(CH_3)_2$	12	87	oil
CLXXXVI	$(CH_2)_2N(CH_3)_2$	8	78	oil
CLXXXVII	$(CH_2)_3$-N 	6	73	170-172
CLXXXVIII	$(CH_2)_3$-N 	6	84	131-131.5
CLXXXIX	$(CH_2)_3$-N 	8	88	114-115

since the final product will maintain two aromatic π-electron systems. Alkylation at the N^3-site would result in a less stable product having only a single aromatic ring system.



N^{10}-anion

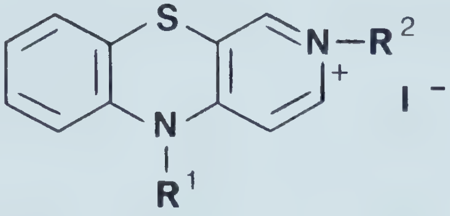
N^3-anion

3.7.2.0.0 Preparation of 10-dialkylaminoalkyl-10H-pyrido-[3,4-b][1,4]benzothiazine oxalates and 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates.

Anhydrous oxalic acid and 10-(2-dimethylaminoethyl)-10H-pyrido-[3,4-b][1,4]benzothiazine (CLXXXVI) were heated at reflux in absolute ethanol to give 10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXC). Subsequent treatment of CXC with excess methyl iodide afforded 3-methyl-10-(2-dimethylaminoethyl)-10H-pyrido-[3,4-b]]1,4]benzothiazinium iodide oxalate (CXCI) in 90% yield. Other 10-dialkylyaminoalkyl-10H-pyrido[3,4-b][1,4]-benzothiazine oxalates and 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates were prepared in a similar manner. The synthetic data is presented in Table XIV.

Addition of oxalic acid to 10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXVI) results in salt formation at the more basic terminal nitrogen atom. The terminal methyl group and the alpha terminal amino methylene group of CXC are both deshielded by 0.6 δ relative to the corresponding groups in CLXXXVI. The nmr spectrum(δ) of 3-methyl-10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]-benzothiazinium iodide oxalate (CXCI) shows a downfield shift of 0.3 and 0.2 δ for the C-4 and C-2 protons respectively. Treatment of CXC with methyl iodide results in methyl iodide

Table XIV: Synthetic data for 10-dialkyaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazine oxalates and 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazine iodide oxalates.



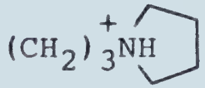
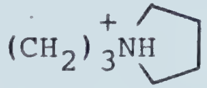
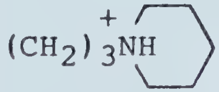
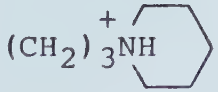
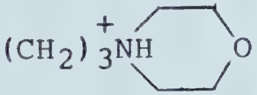
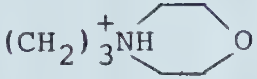
Compd	$R^{1\,a}$	$R^{2\,b}$	% yield	mp(°C)
CXC	$(CH_2)_2\overset{H}{\underset{+}{N}}(CH_3)_2$ ox$^-$	-	100	204-206
CXCI	$(CH_2)_2\overset{H}{\underset{+}{N}}(CH_3)_2$ ox$^-$	CH_3	90	250
CXCII	$(CH_2)_3\underset{+}{NH}(CH_3)_2$ ox$^-$	-	100	146-148
CXCIII	$(CH_2)_3\underset{+}{NH}(CH_3)_2$ ox$^-$	CH_3	76	189-191
CXCIV	 ox$^-$	-	98	129-131
CXCV	 ox$^-$	CH_3	90	233-235
CXCVI	 ox$^-$	-	100	161-163
CXCVII	 ox$^-$	CH_3	100	205-207

Table XIV: Continued

Compd	R^{1a}	R^{2b}	% yield	mp(°C)
CXCVIII	 ox^-	-	96	162-164
CIC	 ox^-	CH_3	92	213-215

[a] ox^-, oxalate ($^-O_2CCO_2H$). [b] When no R^2 substituent is present, the I^- ion is not present.

salt formation at the most basic nitrogen centre, the N^3-position. The deshielding of the C-2 and C-4 protons presented above correspond to the structure CXCI.

It was necessary to synthesize the methyl iodide-oxalate salts of 10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]-benzothiazines prior to reduction with sodium borohydride. Treatment of 10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXXVI) with methyl iodide results in methylation at the N^3-and the N^{10}-side chain terminal nitrogen atom. Subsequent reaction of this dimethyl iodide salt would not afford the desired product having a dimethylaminoethyl functionality attached to N-10.

3.7.3.0.0 Reaction of 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates with sodium borohydride.

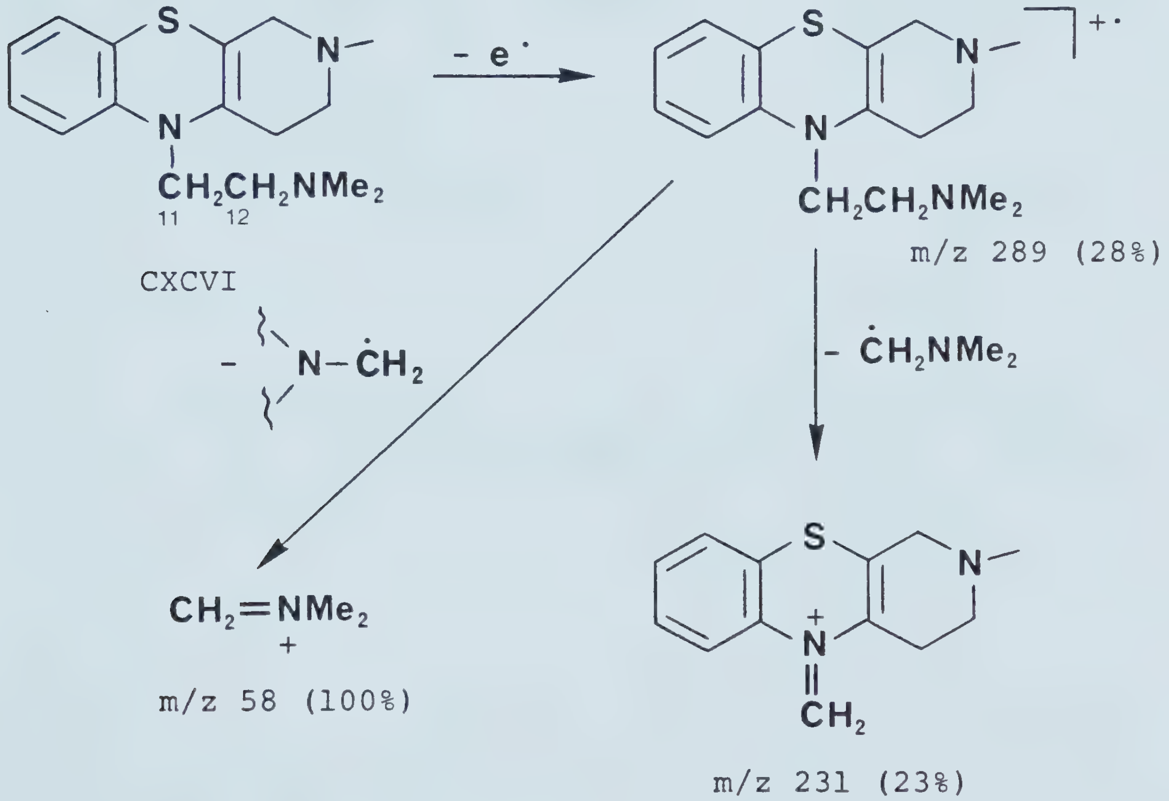
Reduction of pyridinium salts with sodium borohydride generally leads to tetrahydropyridines[98,99] although dihydropyridines[298] and piperidines[299,300] have been reported. It was therefore expected that 3-methyl-10-diaklylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates would react with sodium borohydride to give dihydropyridine, tetrahydropyridines or piperidine derivatives or a mixture of these products.

Addition of sodium borohydride to a suspension of 3-methyl-10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]-benzothiazinium iodide oxalate (CXCI) in 95% ethanol afforded 3-methyl-10-(2-dimethylaminoethyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CC) in 67% yield. The synthetic data for the reduction of other 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates with sodium borohydride is listed in Table XV.

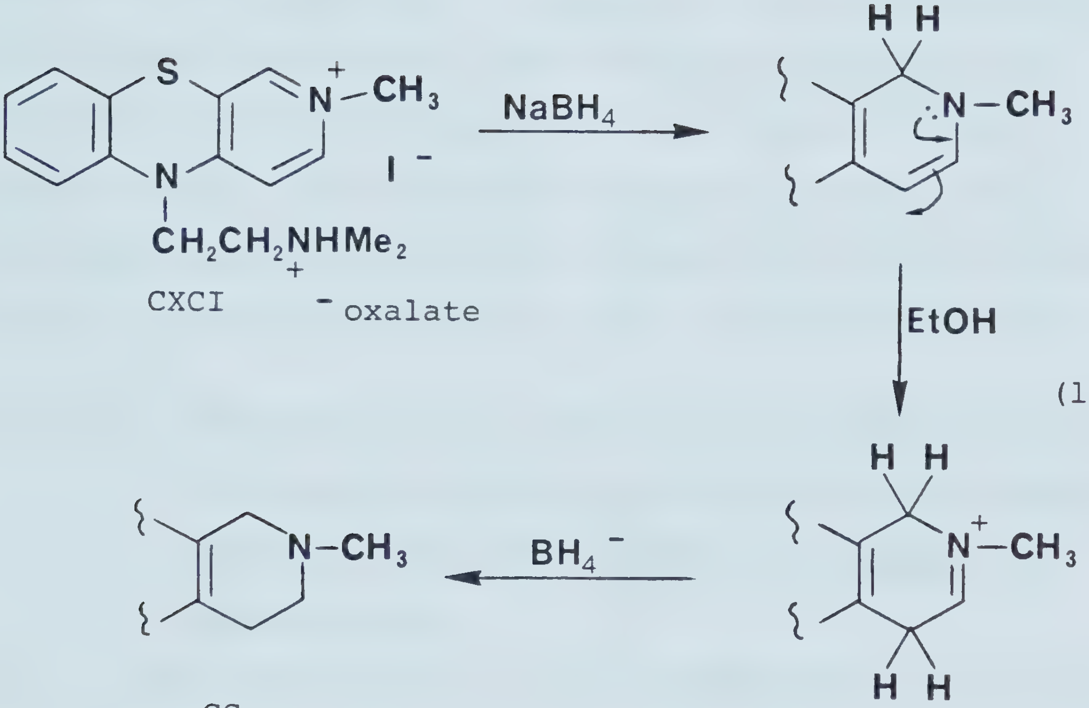
The nmr spectrum(δ) of CC exhibits a 19H multiplet between 2.1 and 4.4 due to the N^3-methyl, $N(CH_3)_2$,C_1-H, C_2-H,C_4-H,C_{11}-H and C_{12}-H, and a 4H multiplet at 7.1 attributed to the C_6-C_9-H. The ir spectrum shows the presence of an olefin functionality at 1590 cm^{-1}. The mass spectrum of CC exhibits a molecular ion at m/z 289 (Exact mass calc'd for $C_{16}H_{23}N_3{}^{32}S$: 289.1616; found (high resolution ms): 289.1607). Fragmentation of the molecular ion occurs by two major pathways (Scheme XI). Loss of a trimethylamine radical gives rise to a peak at m/z 231 ($C_{13}H_{15}N_3S^+$). The base peak at m/z 58($C_3H_8N^+$) arises by loss of a 231 amu 3-azaphenothiazine radical.

The mechanism for the sodium borohydride reduction of the pyridinium ring present in CXCI is shown in equation (13). Initial attack of sodium borohydride most likely occurs at the C-4 position of the pyridyl ring in CXCI. Attack of sodium borohydride at the C-2 position of CXCI

Scheme XI: Fragmentations of 3-methyl-10-(2-dimethylaminoethyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CC).



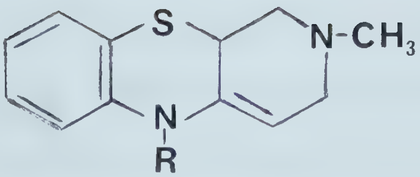
CXCVI



CXCI

CC

(13)



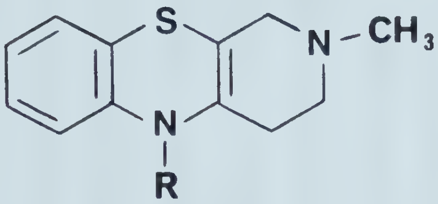
CCI

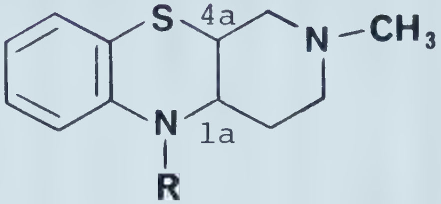
did not occur to produce CCI since no olefinic protons were noted in the nmr spectra. Attack at the C-4 position by sodium borohydride is expected since the sulfur functionality decreases the electron density of the C-4 position relative to the C-2 position. In addition, the 1,2,3,4-tetrahydropyridyl derivative CC has conjugation with the free electrons on the N^{10}-nitrogen and sulfur which is not present in CCI. This extended conjugation gives rise to increased stability of CC and thus may be a factor in the attack of sodium borohydride at the C-4 position of CXCI.

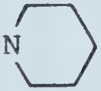
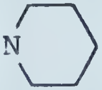
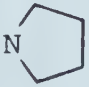
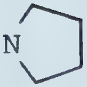
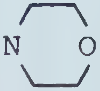
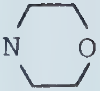
3.7.4.0.0 Hydrogenation of 3-methyl-10-dialkylaminoalkyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4] benzothiazines with 10% palladium on charcoal and hydrogen gas.

The synthesis of 1,2,3,4-tetrahydropyridyl-3-azaphenothiazine analogues (Table XV) was initiated in order to examine the pharmacological activities of these compounds. It was hoped that the tetrahydropyridyl-3-azaphenothiazines would demonstrate pharmacological properties similar to the clinically useful 2-substituted phenothiazines and 1-azaphenothiazines in spite of the fact that the ring systems are very different. The structurally similar hexahydropyridyl-3-azaphenothiazines may also show interesting pharmacological properties. They are readily available by reduction of the olefin group of the corresponding 1,2,3,4-

Table XV: Synthetic data for 3-methyl-10-dialkylaminoalkyl-10H-1,2,3,4-tetrahydro(1,1a,2,3,4,4a-hexahydro)pyrido[3,4-b][1,4]benzothiazines.





Compd	R	% yield	Compd	R	% yield
CC	$(CH_2)_2N(CH_3)_2$	61	CCII	$(CH_2)_2N(CH_3)_2$	38
CCIII	$(CH_2)_3N(CH_3)_2$	57	CCIV	$(CH_2)_3N(CH_3)_2$	37
CCV	$(CH_2)_3$-N 	22	CCVI	$(CH_2)_3$-N 	34
CCVII	$(CH_2)_3$-N 	21	CCVIII	$(CH_2)_3$-N 	29
CCIX	$(CH_2)_3$-N 	20	CCX	$(CH_2)_3$-N 	30

tetrahydropyridyl-3-azaphenothiazine using 10% palladium on charcoal and hydrogen gas.

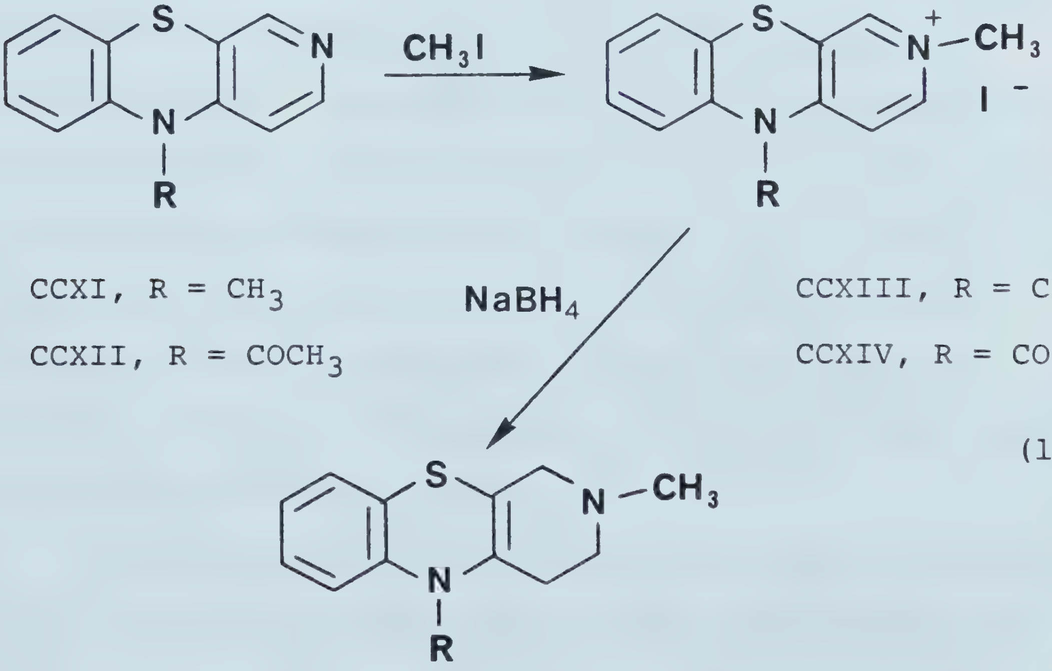
Reaction of 3-methyl-10-(2-dimethylaminoethyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4] benzothiazine (CC) with 10% palladium on charcoal and hydrogen gas for 24 h gave 3-methyl-10-(2-dimethylaminoethyl)-10H-1,1a,1,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCII) in 38% yield. The synthetic data for the reactions of other 3-methyl-10-dialkylaminoalkyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]-benzothiazines with 10% palladium on charcoal and hydrogen gas to afford 3-methyl-10-dialkylaminoalkyl-10H-1,1a,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazines is summarized in Table XV. The nmr, ir and mass spectral data are in accordance with the proposed structures.

3.7.5.0.0 Preparation of 3,10-dimethyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]-benzothiazine (CCXV) and 3-methyl-10-acetyl-10H-1,2,3,4-tetrahydropyrido-[3,4-b][1,4]benzothiazine (CCXVI).

The importance of the N^{10}-side chain in the phenothiazine series in relation to pharmacological properties has been reviewed earlier in the discussion (3.6.0.0.0). Briefly, the length of the N-10 side chain and degree of branching greatly effects the prominent pharmacological properties observed in the phenothiazines. The N^{10}-side chains commonly present in the phenothiazine

series have been incorporated into the 1,2,3,4-tetrahydro- and 1,1a,2,3,4,4a-hexahydro-3-azaphenothiazines (Table XV). A study was initiated to determine the pharmacological effect of structural simplification at the N^{10}-position in the 1,2,3,4-tetrahydro-3-azaphenothiazine series. The preparation of two such compounds where N^{10}-substitution is methyl and acetyl is presented below.

3,10-Dimethyl-10H-1,2,3,4-tetrahydropyrido[3,4-b]-[1,4]benzothiazine (CCXV) and 3-methyl-10-acetyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCVI) were prepared in a manner similar to the 1,2,3,4-tetrahydropyrido-[3,4-b][1,4]benzothiazines (Table XV). The reaction sequence is given in equation (14). 3-Methyl-10H-pyrido-



CCXI, R = CH_3

CCXII, R = $COCH_3$

CCXIII, R = CH_3

CCXIV, R = $COCH_3$

(14)

CCXV, R = CH_3

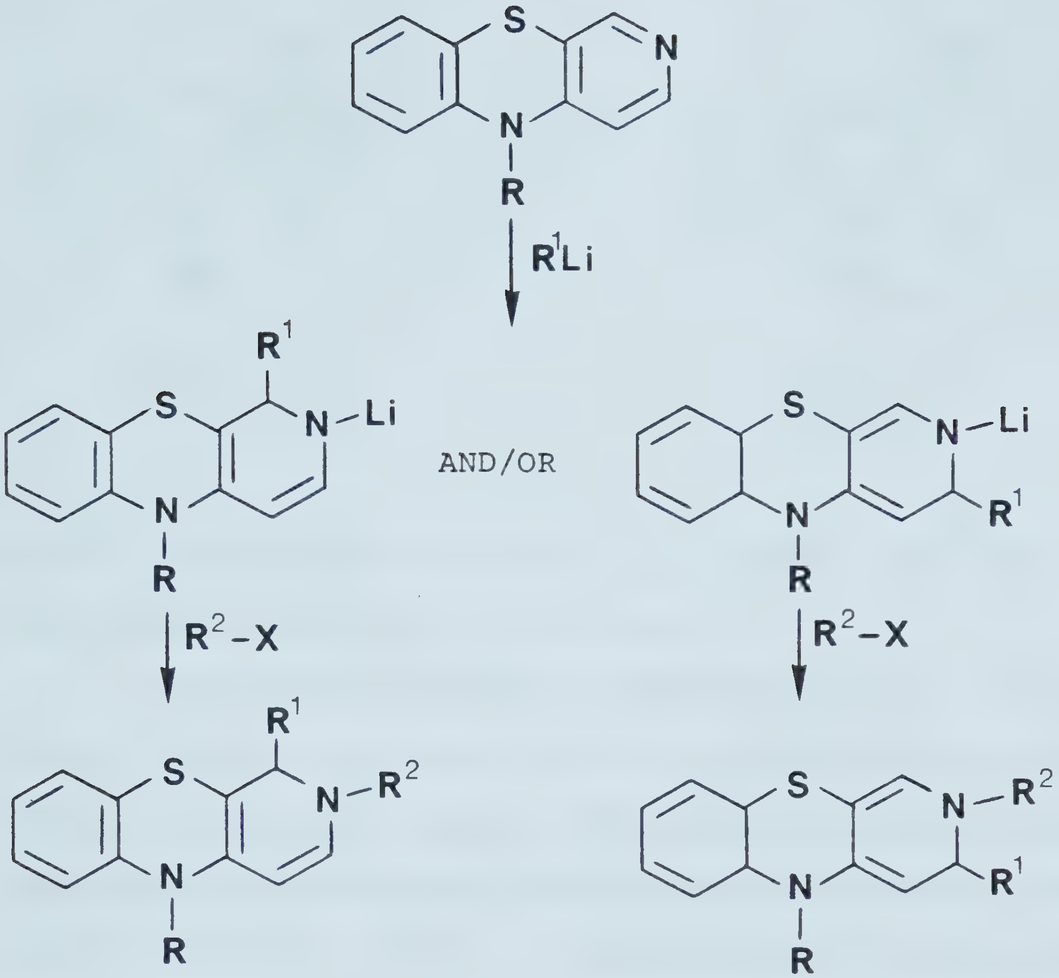
CCXVI, R = $COCH_3$

[3,4-b][1,4]benzothiazine (CXXI) was prepared from the reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) and sodium hydride with methyl iodide while 10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII) was prepared by the reaction of CLXXVI with sodium acetate and acetic anhydride. The structure of the compounds shown in equation (14) are in agreement with their spectral data.

3.8.0.0.0 Reaction of 10-methyl-10H-pyrido[3,4-b][1,4]-benzothiazine (CCXI) with *n*-butyllithium and deuterium oxide.

The reaction of pyridine with organolithium reagents is an efficient method for the synthesis of 1-lithio-2-substituted-1,2-dihydropyridines[301,302]. Subsequent treatment with an appropriate electrophile provides an efficient route to 1,2-disubstituted-1,2-dihydropyridines. It was anticipated that the pyridyl ring of 3-azaphenothiazine would likewise react with a organolithium reagent and an electrophile to produce dihydro-3-azaphenothiazines. The attack of the organolithium reagent could occur at either the C-2 and/or C-4 position and therefore give rise to two isomeric dihydropyridines (15).

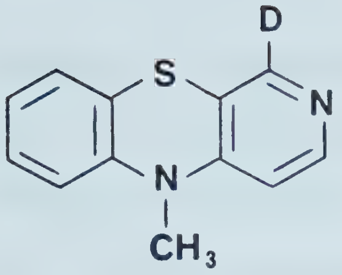
Two moles of *n*-butyllithium were added dropwise to a solution of 10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXI) in tetrahydrofuran followed by addition of excess



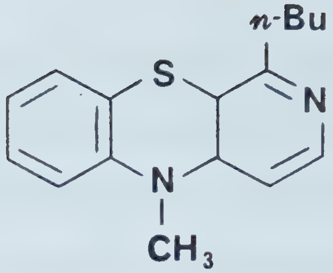
(15)

deuterium oxide. Purification of the crude reaction material using preparative tlc afforded 4-deutero-10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVII) as a red semi-solid in 25% yield and 4-n-butyl-10-methyl-10H-pyrido[3,4-b][1,4]-benzothiazine (CCXVIII) as a red oil in 18% yield.

The nmr spectrum(δ) of CCXVII exhibits a 3H singlet at 3.36 due to the methyl, a 1H doublet ($J_{1,2}$=6Hz) at 6.65 ascribed to the C_1-H, a 4H multiplet at 7.0 due to the C_6-C_9-H, and a 1H multiplet at 8.27 attributed to the C_2-H. The mass spectrum of CCXVII demonstrates a molecular ion at



CCXVII



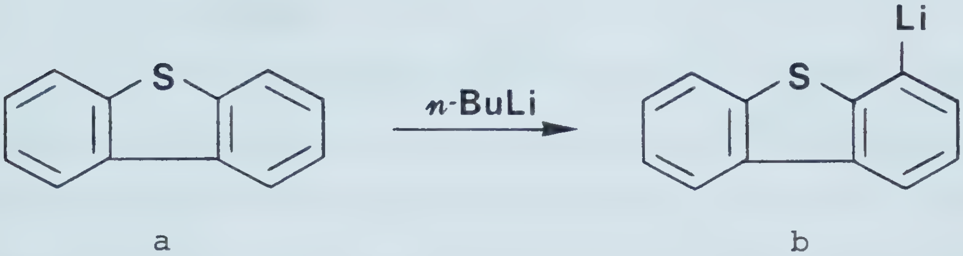
CCXVIII

m/z 215 (Exact mass calc'd for $C_{12}H_{19}DN_2{}^{32}S$: 215.0626; found (high resolution ms): 215.0617).

The nmr spectrum(δ) of CCXVIII exhibits a 7H multiplet at 1.5 and a 2H multiplet at 2.9 due to the respective C_3H_7 and the $\underline{CH_2}C_3H_7$ groups. The remaining proton absorbances are in similar positions to the corresponding resonances observed for CCXVII. Incorporation of a n-Bu group at the C-4 position of CCXVIII is apparent since the C-1 and C-2 proton absorptions remain intact while the C-4 singlet is absent.

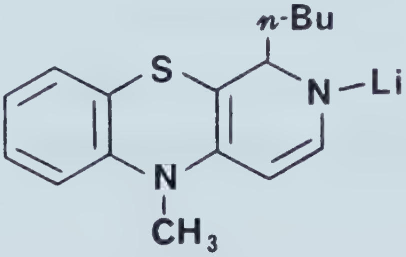
The initial reaction of 10-methyl-10H-pyrido[3,4-b]-[1,4]benzothiazine (CCXI) with n-butyllithium occurs by two processes. Abstraction of the C-4 proton of CCXI by n-butyllithium followed by addition of deuterium oxide leads to the 4-deutero compound CCXVII. The C-4 proton is acidic due to the combined electronic effects of the N^3-nitrogen and the sulfur atom. The sulfur atom has a known ortho-directing influence. Dibenzothiophene (CCXIX-a) reacts with n-butyllithium to give CCXIX-b[303], especially if the

solvent is tetrahydrofuran[304]. It is therefore likely that the sulfur atom in conjunction with the N^3-nitrogen directs metallation to the C-4 position of the pyridyl ring. The 4-n-butyl product CCXVIII is produced by the reaction



CCXIX

mechanism presented earlier in equation (15). Addition of n-butyllithium to the N_3-C_4 bond affords the 3,4-dihydro intermediate CCXX. The 3,4-dihydro derivative subsequently undergoes aromatization to yield CCXVIII. No product resulting from addition of n-butyllithium to the C_2-N_3 bond of CCXI was observed. Addition of n-butyllithium across the N_3-C_4 bond is expected since the C-4 position has a lower electron density than the corresponding C-2 position. An analogous situation was discussed earlier where attack by hydride anion occurs exclusively at the C_4 position of the pyridinium ring present in the 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalates.



CCXX

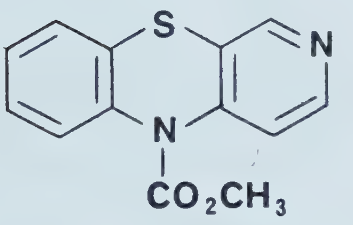
3.9.0.0.0 Reactions of 10H-pyrido[3,4-b][1,4]benzothiazines with diisobutylaluminum hydride and methyl chloroformate or borane-tetrahydrofuran, sodium bis-(2-methoxyethoxy)aluminum hydride and methyl chloroformate.

Minter and Stotter[305] recently described the efficient conversion of quinolines to N-(carboalkoxy)-1,2-dihydroquinolines using two different processes. The first method involves the reaction of quinolines with diisobutylaluminum hydride (DIBAH) followed by treatment with an acylating agent. A complimentary procedure involves the reduction of quinoline-N-boranes with sodium dialkoxyaluminum dihydride at -78°C followed by *in situ* acylation of the intermediate aminoborohydride. It was hoped that 10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]benzothiazines would yield 1,2-dihydroderivatives using these procedures. The resulting dihydrobenzothiazines may possess interesting pharmacological activities.

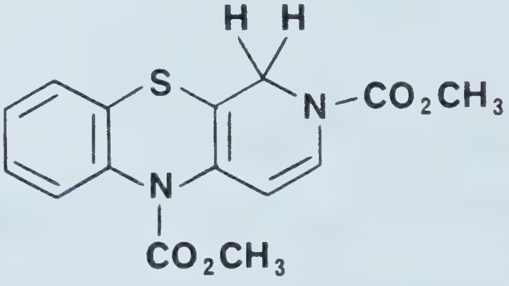
3.9.1.0.0 Treatment of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with diisobutylaluminum hydride (DIBAH) and methyl chloroformate.

Addition of 1.1 equivalent of DIBAH to a suspension of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) in dry tetrahydrofuran followed by addition of excess methyl chloroformate afforded 10-methoxycarbonyl-10H-pyrido[3,4-b][1,4]-

benzothiazine (CCXXI) in 9% yield and bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b][1,4]benzothiazine (CCXXII) in 25% yield. The nmr, ir and mass spectral data for CCXXI are in accordance with the proposed structure. The nmr spectrum(δ) of CCXXII exhibits a 6H singlet at 3.82 accounting for the methyl groups, a 2H multiplet at 4.5 due to the C_4-H, a 1H doublet ($J_{1,2}$=8Hz) at 5.47 attributed to the C_1-H, a 1H multiplet at 6.83 due to the C_2-H and a 4H multiplet at 7.4 assigned to the C_6-C_9-H. The ir spectrum shows the presence of a carbonyl group at 1730 cm^{-1}. The mass spectrum of CCXXII exhibits a molecular ion at m/z 318 (Exact mass calc'd for $C_{15}H_{14}N_2O_4{}^{32}S$: 318.0674; found (high resolution ms): 318.0670).



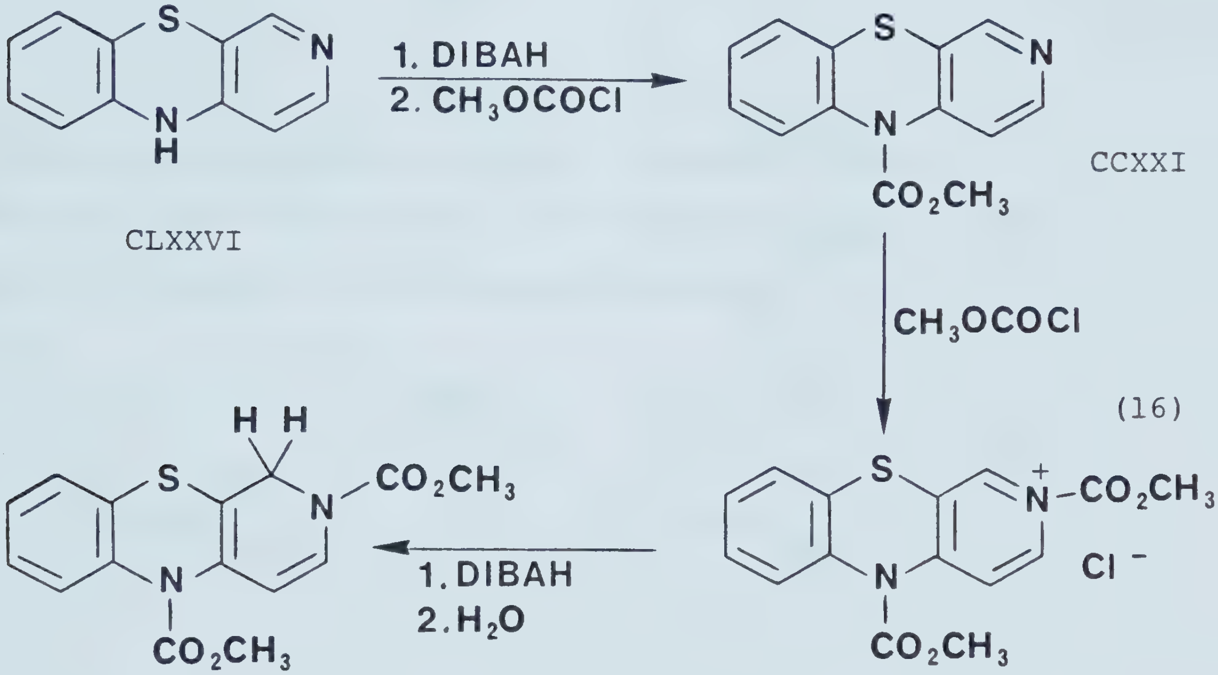
CCXXI



CCXXII

A mechanism for the formation of CCXXI and CCXXII from the reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with DIBAH and methyl chloroformate is given in equation (16). The initial step is complexation of DIBAH with CLXXVI at the N^{10}-position. Subsequent reaction with methyl chloroformate affords the N^{10}-methoxycarbonyl

product CCXXI. Further reaction of CCXXI with methyl chloroformate results in formation of the intermediate pyridinium salt CCXXIII. Subsequent reaction with DIBAH and quenching with water would give CCXXII.



CLXXVI

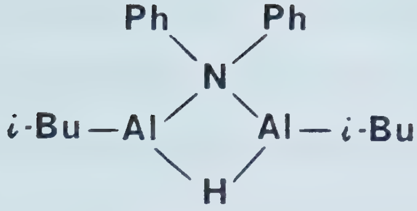
CCXXI

(16)

CCXXII

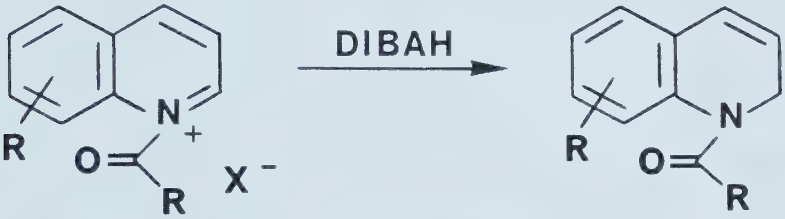
CCXXIII

Reaction of diphenylamine with diisobutylaluminum hydride proceeds rapidly to afford compound CCXXIV[306]. It is therefore not unexpected that CLXXVI undergoes complexation with DIBAH at the N^{10}-secondary amine site. Addition of methyl chloroformate to the CLXXVI-DIBAH complex would then give CCXXI. In the reaction sequence proceeding from CCXXIII to CCXXII, DIBAH serves as a reducing agent in a manner previously described for the sodium borohydride reduction of 3-methyl-10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]-



CCXXIV

benzothiazinium iodide oxalates. Neumann[307] has described the synthesis of 1,2-dihydroquinolines by the action of DIBAH on N-acylquinolinium salts (17).

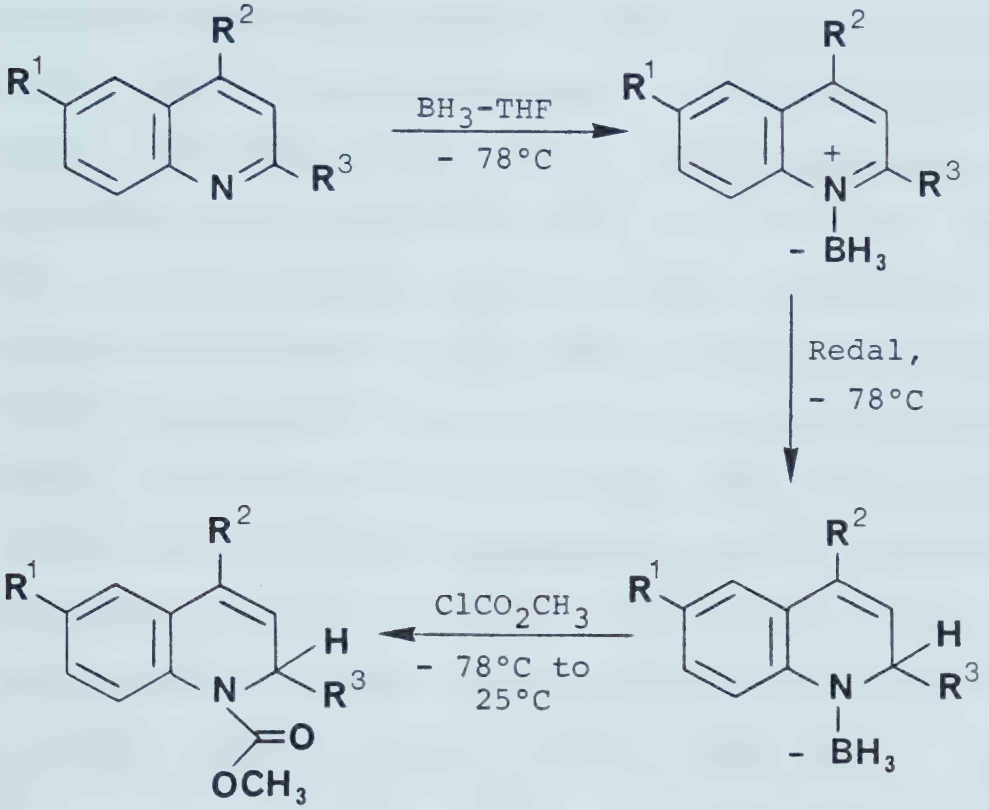


(17)

3.9.2.0.0 Treatment of 10H-pyrido[3,4-b][1,4]benzothiazine with borane-tetrahydrofuran, sodium bis-(2-methoxyethoxy)aluminum hydride and methyl chloroformate.

In the above discussion, the DIBAH-methyl chloroformate procedure of Minter and Stotter[305] was used to synthesize dihydropyridine derivatives of 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI). An alternate route to dihydropyridyl derivatives of CLXXVI is via the use of borane-tetrahydrofuran, sodium bis-(2-methoxyethoxy)aluminum

hydride (Redal) and methyl chloroformate. Minter and Stotter[305] have synthesized 1,2-dihydroquinolines starting from quinolines in 85-90% yields using borane-tetrahydrofuran, Redal and methyl chloroformate (18).



(18)

Reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with borane-tetrahydrofuran, Redal and methyl chloroformate in dry tetrahydrofuran gave 10-methoxycarbonyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXXI) in 4% yield and bis-(3,10-methoxycarbonyl)-3,4-dihydropyrido-[3,4-b][1,4]benzothiazine (CCXXII) in 38% yield. The spectral data (nmr and ir) for CCXXI and CCXXII were identical to those obtained from the reaction of CLXXVI with DIBAH and methyl chloroformate.

The mechanism for the formation of CCXXI and CCXXII from the reaction of CLXXVI with borane-tetrahydrofuran, Redal and methyl chloroformate is similar to that previously discussed for the reaction of CLXXVI with DIBAH and methyl chloroformate (16). The initial step is likely complexation of borane at the N^{10}-position of CLXXVI. Borane displays weaker electron attracting capabilities than aluminum hydrides[308] yet it likely complexes with the N^{10}-secondary amine of CLXXVI. Addition of methyl chloroformate to the CLXXVI-borane complex gives 10-methoxycarbonyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXXI). Further addition of methyl chloroformate affords CCXXIII which in turn is reduced by Redal to give CCXXII in the manner described previously [see equation (16)]. The product CCXXI can only arise by an initial reaction of DIBAH or borane-tetrahydrofuran at the N^{10}-position.

3.9.3.0.0 Reaction of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,4-b][1,4]benzothiazine (CXII) with (a) diisobutylaluminum hydride and methyl chloroformate and (b) borane-tetrahydrofuran, sodium bis-2-(methoxyethoxy)aluminum hydride and methyl chloroformate.

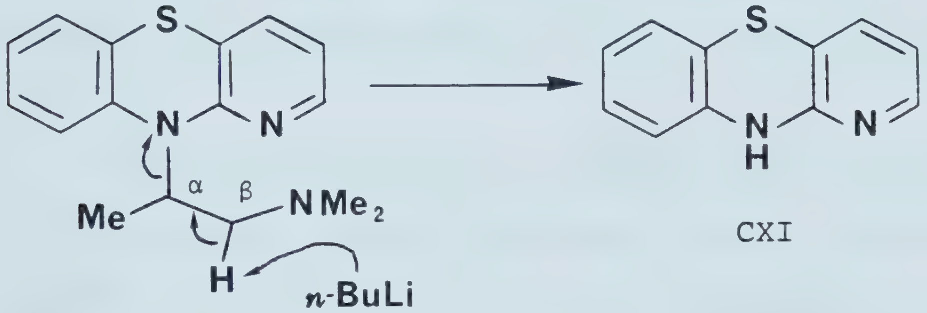
The proposed mechanism for the reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with DIBAH is initial complexation with the secondary amine at the N^{10}-

position (see 3.9.1.0.0). In spite of the likelihood of DIBAH reacting with the terminal amino nitrogen of 10-dialkylaminoalkyl-3-azaphenothiazines it was hoped that reaction of DIBAH would occur only at the N^3-position. The pharmacological properties of the desired 10-dialkylaminoalkyl-dihydro-3-azaphenothiazines would be of interest since the charge distribution of 2-chlorophenothiazines is similar to that of 3,4-dihydro-3-azaphenothiazines.

Addition of 1.1 equivalents of DIBAH and excess methyl chloroformate to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]benzothiazine (CXII) in ether yielded a red intractable oil from which no identifiable product was isolated. The nmr spectrum of the crude reaction material indicated a complete loss of the 10-(3-dimethylaminopropyl) side chain of CXII and did not show the presence of olefinic protons. A similar reaction of CXII, DIBAH and methyl chloroformate in tetrahydrofuran yielded only CXII. The reason for the variation in reaction products in two similar solvents, ether and tetrahydrofuran, is not known. Reaction of CXII with borane-tetrahydrofuran, Redal and methyl chloroformate in tetrahydrofuran also afforded intractable material. The nmr spectrum of the crude reaction material showed a complete loss of the N^{10}-side chain from CXII.

Reactions of 10-dialkylaminoalkyl-3-azaphenothiazines with DIBAH and methyl chloroformate or borane-tetra-

hydrofuran, Redal and methyl chloroformate failed to produce dihydropyridine derivatives directly. The hydride reagents used in the reactions likely decompose the N^{10}-dialkylaminoalkyl side chain. Abstraction of the β-hydrogen of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]-benzothiazine by n-butyllithium and elimination to give 1-azaphenothiazine (CXI) (19)[272]. Alternatively, CXI may arise by attack of n-butyllithium at the α-carbon of 10-(1-methyl-2-dimethylaminoethyl)-10H-pyrido[3,2-b][1,4]benzothiazine. It is possible that DIBAH and Redal may react in a similar manner and undergo a reaction in the N^{10}-side chain of CXII.



(19)

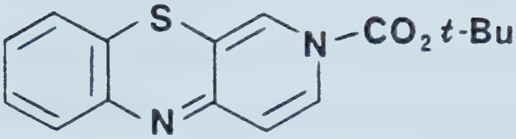
A viable alternative to the synthesis of dihydro-3-azaphenothiazines possessing 10-dialkylaminoalkyl side chains is a protection-deprotection step. Reaction of a 10-protected-3-azaphenothiazine with DIBAH and methyl chloroformate should give a dihydropyridine derivative. Removal of the N^{10}-substitent and alkylation at the same position would produce the target products.

3.10.0.0.0 Reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with sodium hydride and tert-butoxycarbonyl azide.

A possible protecting agent for the N^{10}-nitrogen of 3-azaphenothiazine is a *tert*-butoxycarbonyl group. The *tert*-butoxycarbonyl group is usually stable to base and is removed using mild acidic conditions[309]. Reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) and sodium hydride with *tert*-butoxycarbonyl azide was expected to give the required 10-*tert*-butoxycarbonyl-3-azaphenothiazine. The desired product from the treatment of CLXXVI with sodium hydride and *tert*-butoxycarbonyl azide however was not obtained. The isomeric compound 3-*tert*-butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV) was isolated in 88% yield.

The nmr spectrum(δ) of CCXXV exhibits a 9H singlet at 1.5 accounting for the *tert*-butyl group, a 2H doublet ($J_{1,2}$=8Hz) at 6.78 due to the C_1-H, a 5H multiplet at 6.9 attributed to the C_4-H,C_6-C_9-H and a 1H doublet ($J_{1,2}$=8Hz) of doublets ($J_{2,4}$=1.5 Hz) at 7.32 due to the C_2-H. The ir spectrum of CCXXV showed the presence of a carbonyl group at 1720 cm^{-1}. The mass spectrum of CCXXV exhibits a molecular ion at m/z 300 (Exact mass calc'd for $C_{16}H_{16}N_2O_2{}^{32}S$: 300.0933; found (high resolution ms): 300.0930).

Abstraction of the N^{10}-proton of CLXXVI with sodium hydride as indicated previously in the discussion yields a species which may localize the charge on the N^3-



CCXXV

or N^{10}-position. Most alkylating and acylating reagents add to the N^{10}-anion of CLXXVI to afford 10-substituted-3-azaphenothiazines. It is likely that CCXXV is formed exclusively in the reaction of CLXXVI N^{3}-anion with tert-butoxycarbonyl azide because of steric interactions that the N^{10}-anion of CLXXVI encounters when it approaches the azide. This maybe due to the puckered conformation of the 3-azaphenothiazine ring system. Dreiding molecular models indicate that reaction of the N^{3}-anion of CLXXVI with tert-butoxycarbonyl azide is sterically more favorable than reaction with the N^{10}-anion.

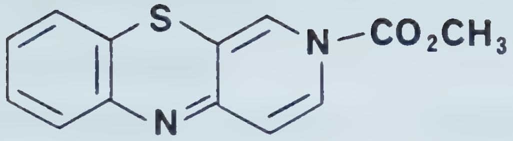
The N^{3}-tert-butoxycarbonyl amide bond present in 3-tert-butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV) is very labile since purification of CCXXV using neutral Alumina column chromatography with methylene chloride-methanol (10:1 v/v) as eluant gave 10H-pyrido[3,4-b][1,4]-benzothiazine (CLXXVI) as the only product.

3.11.0.0.0 Reaction of 10-acetyl-10H-pyrido[3,4-b][1,4]-benzothiazine (CCXVI) with diisobutylaluminum hydride and methyl chloroformate.

Previous results in the discussion have shown that 3-azaphenothiazine (CLXXVI) undergoes reaction with DIBAH and methyl chloroformate to give 3,10-bis(methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b][1,4]benzothiazine (CCXXII). It was hoped that protection of the N^{10}-position of 3-azaphenothiazine and reaction with DIBAH-methyl chloroformate would give a dihydropyridine compound. Removal of the N^{10}-protecting group and subsequent N^{10}-alkylation would give the target dihydropyrido[3,4-b][1,4]-benzothiazines. Another potential N^{10}-protecting group is the acetyl functionality which can be easily removed later using base.

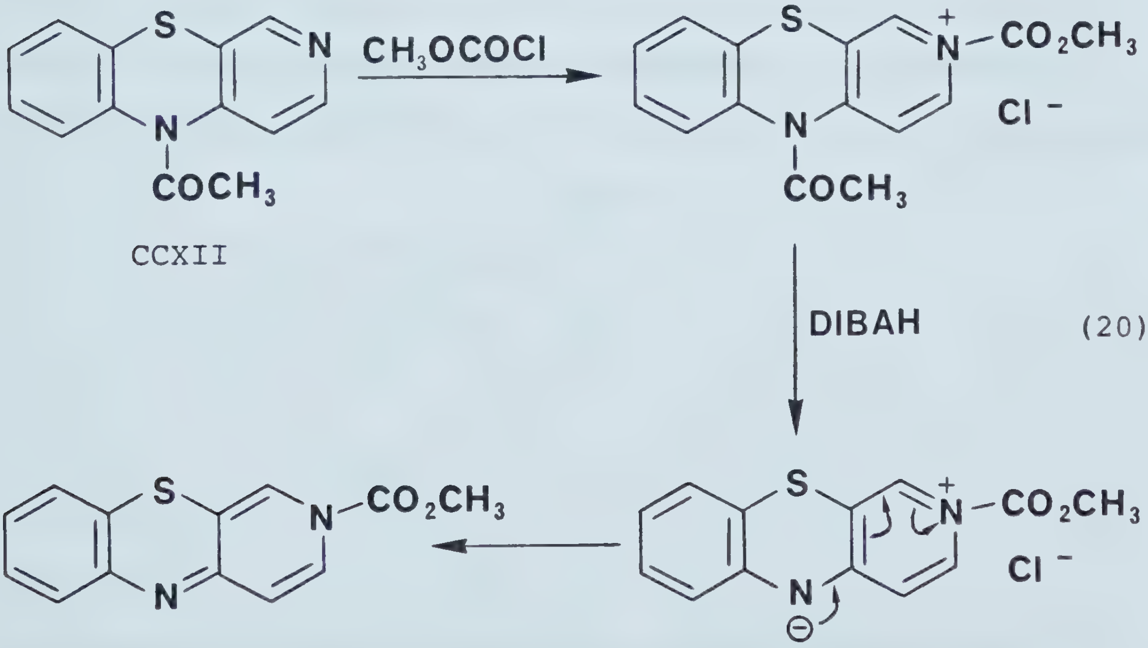
Addition of DIBAH and methychloroformate to a solution of 10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVI) in dry tetrahydrofuran gave 3-methoxycarbonyl-3H-pyrido-[3,4-b][1,4]benzothiazine (CCXXVI) in 90% yield. The nmr, ir and mass spectral data for CCXXVI are consistent with the assigned structure.

Initially, 10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII) reacts with methyl chloroformate to produce a quaternary pyridinium salt at the N^3-position (20). The reagent DIBAH then cleaves the N^{10}-acetyl group to give an anion at the N^{10}-position (CCXXVII). The structure



CCXXVI

CCXXVII stabilizes itself by conjugation to give CCXXVI. Cleavage of the N[10]-acetyl functionality by DIBAH is not surprising since the reaction of 10-acetylphenothiazine with n-butyllithium gives rise to the parent phenothiazine[311].



CCXII

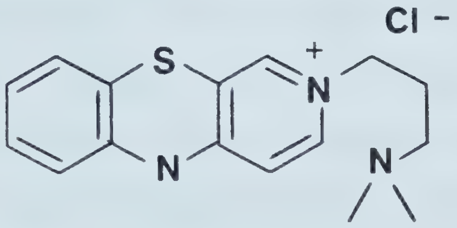
(20)

CCXXVI

CCXXVII

3.12.0.0.0 Pharmacological testing of 3-azaphenothiazine derivatives.

Phenothiazines exhibit a variety of pharmacological actions including antipsychotic, antihistaminic, antiemetic and sedative properties. Clearly the phenothiazines possess a complex pharmacological spectrum affecting many processes in the body. Some 1-azaphenothiazines which are of clinical importance include prothipendyl, pervetral and pipazethate. These compounds are marketed as antihistaminic, antiemetic and antitussive agents respectively. Clarke and coworkers[270] have shown that the 3-azaphenothiazinum chloride CII is a potent hypotensive agent. The previously unknown reduced pyridyl 3-azaphenothiazines are therefore an interesting class of compounds with potential pharmacological activities.



CII

3.12.1.0.0 Analgesic properties of 3-azaphenothiazine derivatives.

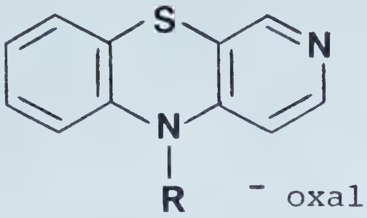
The analgesic activities for the compounds whose preparation was discussed previously were determined using the phenylquinone writhing test[290]. The results are

summarized in Table XVI. All mice were sedated when the inhibition was greater than 75%. In those cases where inhibition was 75% or less, the mice were either partially sedated or behaved in a manner similar to predosing.

The 10-dialkylaminoalkyl-10H-pyrido[3,4-b][1,4]-benzothiazine oxalates listed in Part A of Table XVI demonstrated a mild analgesic response. The pyrrolidinyl compound CXCIV showed the best activity by exhibiting a 61% inhibition at a 5 mg/kg sc dose.

The analgesic values for the tetrahydropyridyl compounds CCXV, CCXVI, CC, CCIII, CCV, CCVIIand CCIX are presented in Part B of Table XVI. A range of analgesic potencies were observed. Those compounds whose R-substituent is methyl (CCXV) and pyrrolidinylpropyl (CCVII) exhibit the lowest activities. It is interesting to note that the pyrrolidinyl compound shown in Part A of Table XVI was the most active member of that series while the pyrrolidinyl derivative CCVII shown in Part B of Table XVI was the least potent member of the tetrahydropyridine group. The morpholino compound CCIX shown in Part B of Table XVI exhibits significant analgesic properties. The ED_{50} for CCIX is 0.013 mg/kg sc in mice, one third that of morphine sulfate. The mechanism by which CCIX elicits its analgesia is not known. It is likely that a narcotic receptor site is not involved, as the structural requirements for narcotic analgesics described earlier for the piperidylidene

Table XVI: Analgesic properties of 3-azaphenothiazine derivatives.



- oxalate

PART A

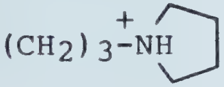
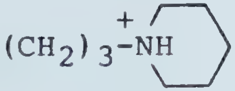
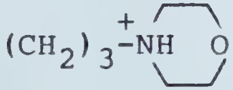
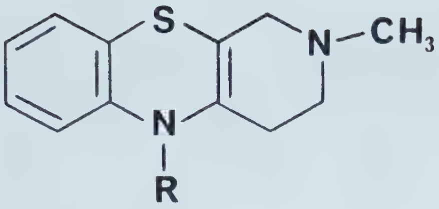
Compd	R	Dose (mg/kg sc)[a]	% Inhib[b]
CXC	$(CH_2)_2\overset{+}{N}H(CH_3)_2$	20	59 ± 9
CXCII	$(CH_2)_3\overset{+}{N}H(CH_3)_2$	20	78 ± 7
CXCIV	 $(CH_2)_3\text{-}\overset{+}{N}H$	20	86 ± 10
		5	61 ± 11
CXCVI	 $(CH_2)_3\text{-}\overset{+}{N}H$	20	72 ± 8
CXCVIII	 $(CH_2)_3\text{-}\overset{+}{N}H$ O	20	59 ± 12

Table XVI: Continued



PART B

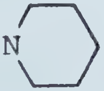
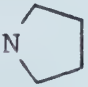
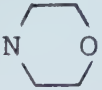
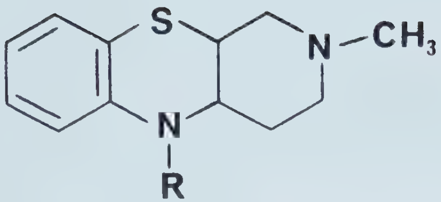
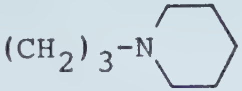
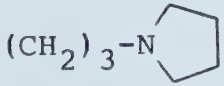
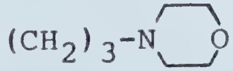
Compd	R	Dose (mg/kg sc)[a]	% Inhib[b]
CCXV	CH_3	10	54 ± 7
CCXVI	$COCH_3$	10	69 ± 9
CC	$(CH_2)_2N(CH_3)_2$	10	67 ± 10
CCIII	$(CH_2)_3N(CH_3)_2$	10	67 ± 9
CCV	$(CH_2)_3$-N 	20	68 ± 10
CCVII	$(CH_2)_3$-N 	20	60 ± 7
CCIX	$(CH_2)_3$-N 	20	93 ± 3
		2	69 ± 6
		0.2	54 ± 13
		0.02	38 ± 10
		0.13	ED_{50} ± 6

Table XVI: Continued



PART C

Compd	R	Dose (mg/kg sc)[a]	% Inhib [b]
CCII	$(CH_2)_2N(CH_3)_2$	5 0.5	47 ± 9 27 ± 14
CCIV	$(CH_2)_3N(CH_3)_2$	5 0.5	58 ± 12 38 ± 3
CCVI	 $(CH_2)_3$-N	5 0.5	77 ± 2 46 ± 12
CCVIII	 $(CH_2)_3$-N	5	60 ± 11
CCX	 $(CH_2)_3$-N O	5	47 ± 5

PART D

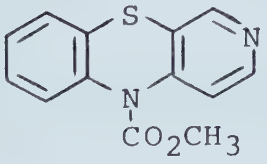
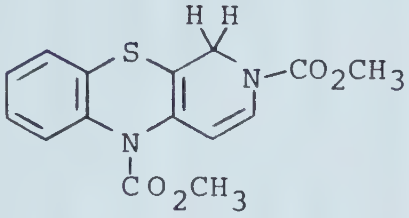
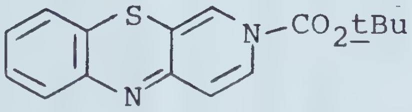
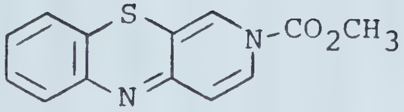
Compd	Structure	Dose (mg/kg sc)[a]	% Inhib
CCXXI		10	40 ± 9

Table XVI: Continued

PART D

Compd	Structure	Dose (mg/kg sc)[a]	% Inhib[b]
CCXXII		10	88 ± 6
		1	74 ± 6
		0.1	47 ± 9
CCXXV		10	84 ± 4
		1	73 ± 3
		0.1	50 ± 7
		0.01	43 ± 5
		0.08	ED_{50} ± 4
CCXXVI		10	69 ± 6
Aspirin™		50	ED_{50}
morphine sulfate		0.038	ED_{50}

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[a] Phenylquinone writhing test. [b] The result is the mean ± SEM for five animals.

analgesics are not present in CCIX.

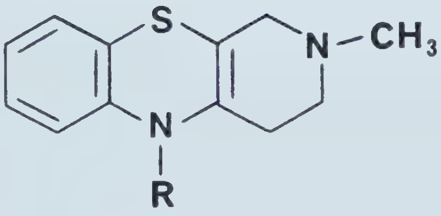
The 1,1a,2,3,4,4a-hexahydropyridyl compounds CCII, CCIV, CCVI, CCVIII and CCX shown in Part C of Table XVI displayed mild analgesia. The morpholino hexahydro compound CCX displayed weak analgetic properties. The most potent compound is likely the piperidinopropyl analogue CCVI whose ED_{50} is likely near 1 mg/kg sc although additional data is required to calculate an accurate value.

3-_tert_-Butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV) (Table XVI) is the most potent analgesic prepared in the 3-azaphenothiazine series. It's ED_{50} (0.08 mg/kg sc) is one-half that of morphine sulfate. At the present time it is not known whether the _tert_-butoxycarbonyl functionality is cleaved _in vivo_. This cleavage may arise since CCXXV is readily converted into 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI) using mild neutral conditions. The structurally related compound 3-methoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXVI) evinces a significantly lower potency than CCXXV. The 3,4-dihydro compound CCXXII also has good analgetic actions. Additional data is required to plot an ED_{50} for bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b][1,4]benzothiazine (CCXXII), however, it is likely about 0.1 mg/kg sc. The good analgesia demonstrated by the structurally unrelated phenothiazines 3-_tert_-butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV) and bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b]-

[1,4]benzothiazine (CCXXII) may be worthy of further investigation.

3.12.2.0.0 Antibacterial properties of 10-dialkylaminoalkyl-10H-1,2,3,4-tetrahydro(1,1a,2,3,4,4a,-hexahydro)pyrido[3,4-b][1,4]benzothiazines.

The screening procedure used is discussed in the experimental. The bacteria used in this screen were *Staphylococcus aureus*, *Streptococcus faecalis* and *Escherichia coli*. The fungi employed were *Candida albicans* and *Saccharomyces cerevisae*. The compounds tested in this assay are listed in Part B and Part C of Table XVI. Compounds CC and CCIII were the only compounds to demonstrate antimicrobial activity. The remaining compounds did not prevent microbial or fungal growth at concentrations of 100, 10 and 1 μg/mL.



CC, R = $(CH_2)_2N(CH_3)_2$

CCIII, R = $(CH_2)_3N(CH_3)_2$

At a concentration of 100 μg/mL CC inhibited the growth of *S. aureus* and *E. coli* after six days. These organisms multiplied in the presence of 10 and 1 μg/mL of CC. No other bacteria or fungi were inhibited by CC. Compound CCIII was

active toward *S. aureus* and *E. coli* at 100 μg/mL after 24 hours at 37°C. This effect was only bacteriostatic in nature since *S. aureus* and *E. coli* multiplied following a further five days incubation in the presence of 100 μg/mL of CCIII.

10-Dialkylaminoalkyl-10H-1,2,3,4-tetrahydro(1,1a,-2,3,4,4a-hexahydro)pyrido[3,4-b][1,4]benzothiazines demonstrate a general lack of antimicrobial and antifungal properties. The 1,2,3,4-tetrahydropyrido compound CC may be worthy of further investigation since it demonstrated activity at 100 μg/mL toward the gram positive organism *S. aureus* and a gram negative organism *E. coli*.

4.0.0.0.0 EXPERIMENTAL

4.1.0.0.0 General considerations.

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide discs unless otherwise specified) were taken on a Perkin Elmer 267 or Unicam SP 1000 spectrophotometer. Nuclear magnetic resonance spectra were recorded for solutions of deuterochloroform with TMS as the internal standard unless otherwise noted. The spectra were recorded on a Varian EM-360A or Bruker Spectrospin 100. Mass spectra were measured with an AEI-MS-9 or Hewlett Packard 5995A mass spectrometer. All of the products described gave rise to a single spot on tlc using three different solvent systems of low, medium and high polarity.

All anhydrous reactions were conducted in pre-dried glassware under a positive nitrogen atmosphere. Dry nitrogen gas was obtained by passage through concentrated sulfuric acid, solid potassium hydroxide and then anhydrous calcium sulfate.

4.1.1.0.0 Solvents and reagents.

Reagent grade toluene was boiled under reflux in the presence of lithium aluminum hydride for four hours and distilled in a closed system for immediate use.

Dry ether and tetrahydrofuran were distilled in the presence of sodium and benzophenone under a nitrogen atmosphere immediately prior to use.

Acetonitrile was purified by stirring in the presence of calcium hydride for two hours prior to distillation and was stored under an atmosphere of nitrogen.

Dimethyl sulfoxide was dried by heating at reflux for three hours in the presence of calcium hydride and was distilled prior to storage over 4A molecular sieves under a nitrogen atmosphere.

1-Alkyl(arylalkyl)-1,2,3,4-tetrahydropyridines were distilled from potassium hydroxide pellets immediately prior to use.

Methanesulfonyl azide was prepared by the reaction of methanesulfonyl chloride with sodium azide using the method described by Stout[89]. Benzenesulfonyl azide, tosyl azide, 4-acetamidobenzenesulfonyl azide, 4-chlorobenzenesulfonyl azide, 4-methoxybenzenesulfonyl azide, 4-nitrobenzenesulfonyl azide, 3-nitrobenzenesulfonyl azide, 2-nitrobenzenesulfonyl azide and benzoyl azide were prepared in a similar manner. The acid hydrolysis of 4-acetamidobenzenesulfonyl azide using the procedure of Cremyln[312] yielded 4-aminobenzenesulfonyl azide. Phenyl azide was obtained using the method reported by Lindsay and Allen[313].

1-Methyl-1,4-dihydropyridine was prepared from the reaction of lithium aluminum hydride with N-methoxycarbonyl-

1,4-dihydropyridine[85] using the procedure described by Fowler[94].

10H-Pyrido[3,4-b][1,4]benzothiazine was prepared using the reaction sequence of Kruger and Mann[314], Takahashi and Ueda[315] and Clarke and co-workers[270].

Potassium *tert*-butoxide was prepared from the reaction of potassium metal with *tert*-butanol and was sublimed under high vacuum (0.1 Torr) prior to use.

Finally, the author gratefully thanks Boehringer-Ingelheim Ltd. for their generous gift of MR-2266((-)2-(3-furylmethyl)-5,9-diethyl-2-hydroxy-6,7-benzomorphan).

4.1.1.1.0 Cyanogen azide.

Cyanogen azide was prepared using the procedure of Marsh[316]. Cyanogen bromide (1.32 g, 0.0125 mol) in 12 mL dry acetonitrile was added slowly with vigorous stirring to a suspension of sodium azide (4.06 g, 0.0625 mol) in 35 mL dry acetonitrile under a nitrogen atmosphere at 0°C. After stirring for 1 h at 0°C the reaction mixture was slowly warmed to 25°C during a 2 h period. The reaction mixture was maintained at 25°C for 1 h after which the supernatant was transferred using a syringe to a second vessel under a nitrogen atmosphere.

4.1.1.2.0 Pyridine-3-sulfonyl azide.

Pyridine-3-sulfonic acid (5.0 g, 0.031 mol) and phosphorus pentachloride (16 g) were heated for 2 h at 130°C

using an oil bath. The liquified mass was carefully poured onto 300 mL ice water, extracted with chloroform (3 x 75 mL), dried (sodium sulfate) and the solvent removed in vacuo to give pyridine-3-sulfonyl chloride as a yellow oil (3.27 g, 59%).

A solution of sodium azide (1.1 g, 0.017 mol) in water (20 mL) was slowly added to a solution of pyridine-3-sulfonyl chloride (2.5 g, 0.014 mol) in 95% ethanol (30 mL) at 0°C with stirring. The reaction was stirred for 2 h and 50 mL water was added. Extraction with methylene chloride (3 x 75 mL), drying (sodium sulfate) and removal of the solvent in vacuo afforded pyridine-3-sulfonyl azide as a yellow oil (2.51 g, 97%): ir (NaCl film) 2140 cm^{-1} (CN); nmr, δ 7.75(d($J_{4,5}$=8Hz) of d($J_{5,6}$=6Hz),1,C_5-H), 8.49(d($J_{4,5}$=8Hz) of d($J_{4,6}$=1.5Hz) of d($J_{2,4}$=1.5Hz),1,C_4-H), 9.13(d($J_{5,6}$=6Hz) of d($J_{4,6}$=1.5Hz),1,C_6-H),9.26(d($J_{2,4}$=1.5Hz),1,C_2-H); Exact mass calc'd for $C_5H_4N_4O_2{}^{32}S$: 184.0054; found (high resolution ms): 184.0052.

4.2.1.1.0 2-Methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (CXIV). General Procedure A.

A solution of cyanogen azide (0.32 g, 4.7 mmol) in 30 mL acetonitrile, prepared from cyanogen bromide (0.50 g, 4.7 mmol) and sodium azide (1.53 g, 23.5 mmol) as reported previously (4.1.1.1.0) was added slowly with stirring to a

solution of 1-methyl-1,4-dihydropyridine (XLIII) (0.45 g, 4.7 mmol) in 75 mL ether at 25°C. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 2 h. Removal of solvent *in vacuo* afforded 2-methyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-3-ene (CXIV)(0.625 g, 99%): mp, 67-69°C; ir, 1665 (C=C), 2190 cm^{-1} (C≡N); nmr, δ 2.20-2.68(m,2,C_5-H),2.9-3.26(m,2,C_1-H, C_6-H),3.3(s,3,CH_3), 5.32-5.7(m,1,C_4-H), 6.25(d($J_{3,4}$=8Hz) of d($J_{3,5}$=2Hz), of d($J_{3,5}$=2Hz),1,C_3-H); Exact mass calc'd for $C_7H_9N_3$: 135.0796; found (high resolution ms): 135.0797; *Anal.* calc'd for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09; found: C, 61.79; H, 6.63; N, 31.19.

4.2.1.2.0 2-Methyl-7-methanesulfonyl-2,7-diazabicyclo-[4.1.0]hept-3-ene (CXV).

A solution of methanesulfonyl azide (0.39 g, 3.2 mmol) in 50 mL ether was added to a solution of 1-methyl-1,4- dihydropyridine (XLIII)(0.30 g, 3.2 mmol) in 50 mL ether at 25°C according to General Procedure A.

Evaporation of the solvent *in vacuo* afforded 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXV)(0.58 g, 96%) as a white solid: mp, 70-72°C; ir, 1670 cm^{-1}(C=C); nmr, δ 2.05-2.55(m,2,C_5-H), 3.00-3.40 (m,8,SO_2CH_3,NCH_3,C_1-H,C_6-H), 5.20-5.52(m,1,C_4-H), 6.10 (d($J_{3,4}$=8Hz) of d($J_{3,5}$=2Hz) of d($J_{3,5}$=2Hz),1,C_3-H); Exact mass calc'd for $C_7H_{12}N_2O_2{}^{32}S$: 188.0619; found (high

resolution ms): 188.0614; Anal. calc'd for $C_7H_{12}N_2O_2S$: C, 44.53; H, 6.41; N, 14.84; found: C, 43.27; H,6.27; N, 14.58.

4.2.1.3.0 2-Methyl-7-benzenesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVI).

A solution of benzenesulfonyl azide (0.58 g, 3.2 mmol) in 75 mL ether was added slowly to a solution of 1-methyl-1,4-dihydropyridine (XLIII)(0.30 g, 3.2 mmol) in 75 mL ether according to General Procedure A. The solvent was evaporated *in vacuo* to afford 2-methyl-7-benzenesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVI)(0.78 g, 98%) as a white solid: mp, 57-59°C; ir, 1665 cm^{-1}(C=C); nmr, δ 2.10-2.50 (m,2,C_5-H),3.02-3.42(m,2,C_1-H ,C_6-H), 3.10(s,3,CH_3), 5.16-5.50(m,1,C_4-H), 6.06(d($J_{3,4}$=8Hz) of d($J_{3,5}$=2Hz) of d($J_{3,5}$=2Hz,1,C_3-H), 7.32-7.78(m,3,C_3-C_5 phenyl hydrogens), 7.88-8.13(m,2,C_2 and C_6 phenyl hydrogens); Exact mass calc'd for $C_{12}H_{14}N_2O_2{}^{32}S$: 250.0776; found (high resolution ms): 250.0780; Anal. calc'd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; found: C, 57.19; H, 5.56; N, 11.17.

4.2.1.4.0 2-Methyl-7-(4-aminobenzenesulfonyl)-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVII).

A solution of 4-aminobenzenesulfonyl azide (0.63 g, 3.2 mmol) in 75 mL ether was added slowly to a solution of

1-methyl-1,4-dihydropyridine (XLIII)(0.30 g, 3.2 mmol) in 75 mL ether at 25°C according to General Procedure A. The solvent was evaporated *in vacuo* to afford 2-methyl-7-(4-aminobenzenesulfonyl)-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVII)(0.82 g, 97%) as a light yellow powder: mp, 188-190°C; ir, 1650 (C=C), 3380 (NH_2), 3480 cm^{-1} (NH_2); nmr, $CDCl_3$/DMSO-d_6, δ 2.00-2.46(m,2,C_5-H), 2.90-3.30(m,2,C_1-H,C_6-H), 3.08 (s,3,CH_3), 4.94(broad s,2,NH_2,exchanges with deuterium oxide), 5.14-5.50(m,1,C_4-H), 6.12(d($J_{3,4}$=8Hz),1,C_3-H), 6.75 (d($J_{2',3'}$=8Hz), 2,*ortho* amino phenyl hydrogens), 7.70(d($J_{2',3'}$=8Hz), 2,*ortho* sulfonyl phenyl hydrogens); Exact mass calc'd for $C_{12}H_{15}N_3O_2{}^{32}S$: 265.0885; found (high resolution ms): 265.0888; *Anal*. calc'd for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70; N, 15.84; found C, 54.04; H, 5.67; N, 15.72.

4.2.1.5.0 2-Methyl-7-(4-acetamidobenzenesulfonyl)-2,7-diazabicyclo[4.1.0]hept-3-ene (CXVIII).

A solution of 4-acetamidobenzenesulfonyl azide (0.77 g, 3.2 mmol) in 75 mL chloroform was added slowly to a solution of 1-methyl-1,4-dihydropyridine (XLIII)(0.30 g, 3.2 mmol) in 75 mL chloroform at 25°C according to General Procedure A.

The solvent was evapoated *in vacuo* to afford 2-methyl-7-(4-acetamidobenzenesulfonyl)-2,7-diazabicyclo[4.1.0]-hept-3-ene (CXVIII)(0.925 g, 94%) as a tan colored solid; mp,

177-179°C; ir, 1655 (C=C), 1710 (C=O), 3380 cm^{-1} (NH); nmr, δ 2.10-2.55(m,2,C_5-H), 2.21(s,3,$COCH_3$), 2.9-3.3(m,2, C_1-H,C_6-H), 3.17(s,3,NCH_3), 5.20-5.55(m,1,C_4-H), 6.12 (d($J_{3,4}$=8Hz) of d($J_{3,5}$=2Hz) of d($J_{3,5}$=2Hz),1,C_3-H), 7.60-8.10(m,4,phenyl hydrogens), 9.14(broad s,1,NH,exchanges with deuterium oxide); Exact mass calc'd for $C_{14}H_{17}N_3O_3{}^{32}S$: 307.0991; found (high resolution ms): 307.0996; Anal. calc'd for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 14.67; found: C, 54.07; H, 5.91; N, 14.30.

4.2.2.0.0 Hydrogenation of 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (CXV).

A mixture of 2-methyl-7-methanesulfonyl-2,7-diazacyclo[4.1.0]hept-3-ene (CXV)(0.05 g, 0.27 mmol) and 10% palladium on charcoal (10 mg) in 95% ethanol (15 mL) were hydrogenated using hydrogen gas at 35 psi. The reaction was allowed to proceed for 6 h after which the mixture was filtered and the solvent removed *in vacuo* to afford 1-methylpiperidylidene-2-methanesulfonamide (CXIX)(0.50 g, 98%) as a white solid. The nmr, ir and micro-tlc of CXIX were identical to an authentic sample (see 4.3.2.1.0).

4.3.0.0.0 1-Methyl-1,2,3,4-tetrahydropyridine (LIII).

1-Methyl-1,2,3,4-tetrahydropyridine was prepared using the procedure of Beeken and Fowler[140]. Freshly sublimed potassium *tert*-butoxide (0.56 g), anhydrous dimethyl

sulfoxide (5.0 mL) and 1-methyl-1,2,3,6-tetrahydropyridine (2.3 g, 23.7 mmol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. The ampule was evacuated using high vacuum (0.2 Torr) and the nitrogen-vacuum process repeated. The ampule was sealed under high vacuum and its contents heated at 90°C for 48 h. The hot contents of the ampule were then added to 4 mL water and quickly extracted with pentane (3 x 25 mL). The combined extracts were dried (sodium sulfate), placed over potassium hydroxide pellets and the pentane removed under a stream of nitrogen to give 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (0.75 g, 33%) as a brown liquid. The nmr spectrum was in agreement with the assignment of Beeken and Fowler[140].

4.3.1.0.0 Reaction of organic azides with 1-substituted-1,2,3,4-tetrahydropyridines: General Procedure B.

A solution containing one mole equivalent of the organic azide in a 10-20 mL volume of ether or methylene chloride was added slowly to a solution of one mole equivalent of the 1-substituted-1,2,3,4-tetrahydropyridine in a small volume of ether at room temperature with stirring. The evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 h. The product was then

filtered and sublimed or recrystallized from the appropriate solvent as described for the individual reactions.

4.3.2.1.0 1-Methylpiperidylidine-2-methanesulfonamide (CXIX).

A solution of methanesulfonyl azide (0.380 g, 3.14 mmol) in 5 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.305 g, 3.14 mmol) in 20 mL ether at 25°C according to General Procedure B. Recrystallization from methylene chloride-ether afforded 1-methylpiperidylidene-2-methanesulfonamide (CXIX)(0.492 g, 82%) as a white solid: mp, 130-131°C; ir, 1590 cm^{-1} (C=N); nmr, δ 1.69-2.00(m,4,C_4-H,C_5-H), 2.93-3.24 (m,8,$SO_2\underline{CH_3}$,$N\underline{CH_3}$,C_3-H), 3.25-3.53(m,2,C_6-H); Exact mass calc'd for $C_7H_{14}N_2O_2{}^{32}S$: 190.0776; found (high resolution ms): 190.0787; Anal. calc'd for $C_7H_{14}N_2O_2S$: C, 44.19; H, 7.42; N, 14.72; found: C, 44.04; H, 7.19; N, 14.85.

4.3.2.2.0 1-Methylpiperidylidene-2-cyanamide (CXXI).

A solution of cyanogen azide prepared from cyanogen bromide (1.32 g, 0.0125 mol) and sodium azide (0.81 g, 0.0125 mol) in 47 mL of dry acetonitrile, as described previously (4.1.1.1.0), was added slowly with stirring to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (0.97 g, 0.01 mol) in 15 mL of dry acetonitrile under a nitrogen atmosphere at 25°C. The evolution of nitrogen gas

was immediate. The reaction was allowed to proceed for 1 h after which the solvent was removed *in vacuo* . Recrystallization from ether-acetonitrile afforded 1-methylpiperidylidene-2-cyanamide (CXXI)(1.11 g, 81%): mp, 98°C; ir, 2190 (C≡N), 1610 cm^{-1} (C=N); nmr, δ 1.73-2.04 (m,4,C_4-H, C_5-H), 2.60-2.87(m,2,C_3-H), 3.04(s,3,CH_3), 3.34-3.58(m,2,C_6-H); Exact mass calc'd for $C_7H_{11}N_3$: 137.0953; found (high resolution ms): 137.0951; *Anal*. calc'd for $C_7H_{11}N_3$: C, 61.29; H, 8.08; N, 30.63; found: C, 60.98; H, 7.94; N, 29.68.

4.3.2.2.1 1-Methyl-2-piperidone (CXXII).

A solution of 1-methylpiperidylidene-2-cyanamide (CXXI) (0.20 g, 1.46 mmol) and 10 mL of 10% sulfuric acid in 100 mL methanol was heated at reflux for 16 h[281]. The solution was neutralized to pH 7 using 10% aqueous sodium hydroxide, filtered and the solution evaporated *in vacuo* to remove the methanol. Extraction of the remaining aqueous mother liquor with chloroform (3 x 50 mL), drying (sodium sulfate) and removal of the solvent *in vacuo* afforded 1-methyl-2-piperidone (CXXII) (0.091 g, 55%) as a tan colored liquid which exhibited ir (NaCl film) and nmr spectra identical to an authentic sample.

4.3.2.3.0 1-Methylpiperidylidene-2-benzenesulfonamide (CXXIII).

A solution of benzenesulfonyl azide (0.55 g, 3.03 mmol) in 10 mL ether was added dropwise to a solution of

1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.294 g, 3.03 mmol) in 20 mL ether at 25°C according to General Procedure B. Recrystallization from methylene chloride-ether afforded 1-methylpiperidylidene-2-benzenesulfonamide (CXXIII)(0.54 g, 71%) as colorless needles: mp, 104°C; ir, 1580 cm^{-1} (C=N); nmr, δ 1.60-1.89(m,4,C_4-H,C_5-H), 2.89-3.20 (m,5,C_3-H,CH_3), 3.20-3.50(m,2,C_6-H), 7.48(m,3,$C_3{}'$-$C_5{}'$ phenyl hydrogens), 7.96(m,2,$C_2{}'$ and $C_6{}'$ phenyl hydrogens). Anal. calc'd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10; found: C,56.80; H, 6.57; N, 11.14.

4.3.2.4.0 1-Methylpiperidylidene-2-(4-methylphenyl)sulfonamide (CXXIV).

A solution of tosyl azide (2.41 g, 12.2 mmol) in 25 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(1.18 g, 12.2 mmol) in 50 mL of ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride afforded 1-methylpiperidylidene-2-(4-methylphenyl)sulfonamide (CXXIV) (2.52 g, 78%) as a white powder: mp, 110-111°C; ir, 1585 cm^{-1} (C=N); nmr, δ 1.60-1.90(m,4,C_4-H,C_5-H), 2.39 (s,3,C_6H_4-$\underline{CH_3}$), 2.92-3.20(m,5,C_3-H,N-CH_3), 3.20-3.47 (m,2,C_6-H), 7.34(d($J_{2',3'}$=8Hz),2,$C_3{}'$and $C_5{}'$ phenyl hydrogens), 7.86(d($J_{2',3'}$=8Hz),2,$C_2{}'$ and $C_6{}'$ phenyl hydrogens). Anal. calc'd for $C_{13}H_{18}N_2O_2S$: C, 58.63 H, 6.81; N, 10.52; found: C, 58.32; H, 6.77; N, 10.60.

4.3.2.5.0 1-Methylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CXXV).

A solution of 4-chlorobenzenesulfonyl azide (1.54 g, 7.1 mmol) in 10 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.69 g, 7.1 mmol) in 20 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-petroleum ether (bp 60-90°C) gave 1-methylpiperidylidene-2-(4-chlorophenyl)-sulfonamide (CXXV)(1.48 g, 73%) as white needles: mp, 106-107°C; ir, 1590 cm^{-1} (C=N); nmr, δ 1.72-2.00 (m,4,C_4-H,C_5-H), 3.00-3.31(m,5,C_3-H,CH_3), 3.30-3.56 (m,2,C_6-H), 7.50(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 8.00(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); Anal. calc'd for $C_{12}H_{15}N_2O_2SCl$: C, 50.25; H, 5.27; N, 9.77: found; C, 49.95; H, 5.21; N, 9.71.

4.3.2.6.0 1-Methylpiperidylidene-2-(4-methoxyphenyl)sulfonamide (CXXVI).

A solution of 4-methoxybenzenesulfonyl azide (1.52 g, 7.1 mmol) in 10 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.69 g, 7.1 mmol) in 30 mL ether at 25°C according to General Procedure B. Sublimation under high vacuum (0.1 Torr, 110°C) afforded 1-methylpiperidylidene-2-(4-methoxyphenyl)sulfonamide (CXXVI)(1.41 g, 70%) as a white powder: mp, 103-105°C; ir, 1585 cm^{-1} (C=N); nmr, δ 1.62-1.93(m,4,C_4-H,C_5-H), 2.90-3.23

(m,5,C_3-H,N-CH_3), 3.23-3.52(m,2,C_6-H), 3.87(s,3,OCH_3), 6.97(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.92 (d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens). Anal. calc'd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92; found: C, 55.10; H, 6.35; N, 9.91.

4.3.2.7.0 1-Methylpiperidylidene-2-(4-nitrophenyl)sulfonamide (CXXVII).

A solution of 4-nitrobenzenesulfonyl azide (1.06 g, 4.65 mmol) in 10 mL methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (0.45 g, 4.64 mmol) in 40 mL ether at 25°C according to General Procedure B.

Recrystallization from carbon tetrachloride-acetone afforded 1-methylpiperidylidene-2-(4-nitrophenyl)sulfonamide (CXXVII)(0.89 g, 65%) as a dark yellow powder: mp, 147-148°C; ir, 1595 cm^{-1} (C=N); nmr, Acetone-d_6,δ 1.83-2.00 (m,4,C_4-H,C_5-H), 2.90-3.21(m,5,C_3-H,CH_3), 3.40-3.70 (m,2,C_6-H), 8.19(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens or $C_{3'}$ and $C_{5'}$ phenyl hydrogens), 8.49(d($J_{2',3'}$=8Hz), 2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens or $C_{3'}$ and $C_{5'}$ phenyl hydrogens); Anal. calc'd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.09; N, 14.13; found: C, 47.89; H, 5.00; N, 13.88.

4.3.2.8.0 1-Methylpiperidylidene-2-(3-nitrophenyl)sulfonamide (CXXVIII).

A solution of 3-nitrobenzenesulfonyl azide (0.97 g, 4.25 mmol) in 15 mL methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (0.41 g, 4.23 mmol) in 30 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-acetone afforded 1-methylpiperidylidene-2-(3-nitrophenyl)sulfonamide (CXXVIII)(554 mg) as a yellow solid. The solvent obtained in the filtration step was evaporated *in vacuo* to afford a yellow solid which was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-acetone (10:1 v/v) as development solvent. Extraction of the fraction having R_f 0.58 using 50 mL hot acetone gave (CXXVIII) (0.257 g). (Total yield of 1-methylpiperidylidene-2-(3-nitrophenyl)sulfonamide was 0.811 g, 65%): mp, 136-137°C; ir, 1590 cm^{-1} (C=N); nmr, Acetone-d_6, δ 1.71-2.08(m,4,C_4-H, C_5-H), 2.90-3.12(m,5,C_3-H,CH_3), 3.40-3.69(m,2,C_6-H), 7.91 (d($J_{4',5'}$=8Hz) of d($J_{5',6'}$=8Hz),1,C_5 phenyl hydrogen), 8.43 (m,2,$C_{4'}$-H phenyl hydrogen,$C_{6'}$ phenyl hydrogen), 8.72 (d($J_{2',4'}$=2Hz) of d($J_{2',6'}$=2Hz),1,$C_{2'}$ phenyl hydrogen); *Anal.* calc'd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.09; N, 14.13; found: C, 48.40; H, 5.11; N, 14.09. Extraction of the fraction having R_f 0.94 using 50 mL hot acetone gave 3-

nitrobenzenesulfonyl azide (0.087 g, 9%), which was identical (nmr and micro-tlc) with an authentic sample.

4.3.2.9.0 1-Methylpiperidylidene-2-(2-nitrophenyl)sulfonamide(CXXIX).

A solution of 2-nitrobenzenesulfonyl azide (1.03 g, 4.52 mmol) in 20 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.44 g, 4.53 mmol) in 30 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-acetone afforded 1-methylpiperidylidene-2-(2-nitrophenyl)sulfonamide (CXXIX)(0.90 g, 67%): mp, 126-127°C; ir, 1585 cm^{-1} (C=N); nmr, Acetone-d_6, δ 1.68-2.19(m,4,C_4-H,C_5-H), 2.82-3.20(m,5,C_3-H,CH_3), 3.40-3.68(m,2,C_6-H), 7.78-7.92 (m,2,C_4' phenyl hydrogen,C_5' phenyl hydrogen), 8.06-8.20 (m,2,C_3' phenyl hydrogen,C_6' phenyl hydrogen); Anal. calc'd for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.09; N, 14.13; found: C, 47.84; H, 4.99; N, 14.19.

4.3.2.10.0 1-Methylpiperidylidene-2-(4-acetamidophenyl)-sulfonamide(CXXX).

A solution of 4-acetamidobenzenesulfonyl azide (0.25 g, 1.04 mmol) in 5 mL methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII)(0.10 g, 1.03 mmol) in 25 mL ether at 25°C

according to General Procedure B. Recrystallization from methylene chloride-ether afforded 1-methylpiperidylidene-2-(4-acetamidophenyl)sulfonamide (CXXX)(0.25 g, 79%) as a yellow powder: mp, 222-223°C; ir, 1710 (C=O), 1595 cm^{-1} (C=N); nmr, Acetone d_6, δ 1.58-1.82(m,4,C_4-H,C_5-H), 2.12(s,3,C(O)CH_3), 2.72-3.12(m,5,C_3-H,NCH_3), 3.22-3.60 (m,3,C_6-H,NH,exchanges with deuterium oxide), 7.81(m,4, phenyl hydrogens); Anal. calc'd for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19; N, 13.58; found; C, 53.81; H, 6.31; N, 13.48.

4.3.2.11.0 1-Methylpiperidylidene-2-(4-aminophenyl)sulfonamide(CXXXI).

A solution of sulfanilyl azide (0.20 g, 1.03 mmol) in 5 mL ether was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (0.10 g, 1.03 mmol) in 20 mL ether according to General Procedure B. Recrystallization from methylene chloride-ether gave 1-methylpiperidylidene-2-(4-aminophenyl)sulfonamide (CXXXI)(0.245 g, 89%) as a light yellow powder: mp, 187-188°C; ir: 3480 (NH_2), 3380 (NH_2), 1590 cm^{-1} (C=N); nmr, δ 1.60-1.89(m,4,C_4-H,C_5-H), 2.90-3.21(m,5,C_3-H,CH_3), 3.21-3.48(m,2,C_6-H), 4.11 (broad s,2,NH_2,exchanges with deuterium oxide), 6.67(d($J_{2',3'}$=8Hz), 2,C_3' and C_5' phenyl hydrogens), 7.73(d($J_{2',3'}$=8Hz),2,C_2' and C_6' phenyl hydrogens); Anal. calc'd for $C_{12}H_{17}N_3O_2S$: C, 53.91; H, 6.41; N, 15.72; found: C, 53.35; H, 6.24; N, 15.64.

4.3.2.12.0 1-Methylpiperidylidene-2-(3-pyridyl)sulfonamide (CXXXII).

A solution of pyridine-3-sulfonyl azide (2.51 g, 13.6 mmol) in 10 mL methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (LIII) (1.32 g, 13.6 mmol) in 35 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-isomeric hexanes afforded 1-methylpiperidylidene-2-(3-pyridyl)sulfonamide (CXXXII)(2.72 g, 79%) as white flakes: mp, 96-97°C; ir, 1600 cm^{-1}(C=N); nmr, δ 1.71-2.02(m,4,C_4-H,C_5-H), 3.03-3.21(m,5,C_3-H,CH_3), 3.21-3.59 (m,2,C_6-H), 7.47(d($J_{5',6'}$=8Hz) of d($J_{4',5'}$=6Hz),1,$C_{5'}$ pyridyl hydrogen), 8.32(d($J_{5',6'}$=8Hz) of d($J_{2',6'}$=2Hz) of d($J_{4',6'}$=2Hz),1,$C_{6'}$ pyridyl hydrogen), 8.81(d($J_{4',5'}$=6Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ pyridyl hydrogen), 9.26(d($J_{2',6'}$=2Hz), 1,$C_{2'}$ pyridyl hydrogen); Anal. calc'd for $C_{11}H_{15}N_3O_2S$: C, 52.16; H, 5.97; N, 16.59; found; C, 51.93; H, 5.99; N, 16.63.

4.3.2.13.1 1-Methylpiperidylidene-2-(3-aminophenyl)sulfonamide (CXXXIII).

A solution of 85% hydrazine hydrate (0.5 mL) and 10% palladium on charcoal (30 mg)[284] was added to a suspension of 1-methylpiperidylidene-2-(3-nitrophenyl)sulfonamide (CXXVIII)(0.20 g, 0.67 mmol) in 30 mL of 95% ethanol at 0°C with stirring. The reaction was then allowed to return to

25°C. The mixture was stirred until the reaction was complete (16 h), as shown by the disappearance of CXXVIII by micro-tlc. The reaction mixture was filtered and water (50 mL) was added to the filtrate. Extraction with methylene chloride (5 x 50 mL), drying (sodium sulfate) and removal of the solvent in vacuo gave a yellow mass. Recrystallization from carbon tetrachloride-acetone afforded 1-methylpiperidylidene-2-(3-aminophenyl)sulfonamide (CXXXIII)(0.14 g, 78%) as light yellow crystals; mp, 165°C; ir, 1590 (C=N), 3370 (NH_2), 3470 cm^{-1} (NH_2); nmr, DMSO-d_6, 1.55-1.86 δ (m,4,C_4-H,C_5-H), 2.74-3.07(m,2,C_3-H), 3.07(s,3,CH_3), 3.19-3.57(m,2,C_6-H), 5.48(broad s,2,NH_2,exchanges with deuterium oxide), 6.69-7.30(m,4,phenyl hydrogens); Anal. calc'd for $C_{12}H_{17}N_3O_2S$: C, 53.91; H, 6.42; N, 15.72; found: C, 53.63; H, 6.38; N, 15.70.

4.3.2.13.2 1-Methylpiperidylidene-2-(2-aminophenyl)sulfonamide (CXXXIV).

10% Palladium on charcoal (75 mg) and 95% hydrazine (1.0 mL) were added to a suspension of 1-methylpiperidylidene-2-(2-nitrophenyl)sulfonamide (CXXIX)(0.44 g, 1.48 mmol) in 45 mL of 95% ethanol at 0°C with stirring. The reaction was allowed to reflux for 12 h. The mixture was filtered and water (50 mL) was added to the filtrate. Extraction with methylene chloride (4 x 75 mL), drying (sodium sulfate) and removal of the solvent in vacuo gave 0.365 g of a thick

green oil. An aliquot (0.35g) was subjected to preparative tlc using ten 20x20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-acetone (5:1 v/v) as the development solvent. Extraction of the lower one-third of the fraction having R_f 0.58 using 75 mL hot acetone gave 1-methylpiperidylidene-2-(2-aminophenyl)sulfonamide (CXXXIV) (0.075 g, 19%) as a light brown solid: mp, 114°C; ir, 1570 (C=N), 3380 (NH_2), 3480 cm^{-1} (NH_2); nmr, Acetone-d_6, δ 1.65-1.98(m,2,C_4-H or C_5-H), 1.98-2.21(m,2,C_4-H or C_5-H), 2.80-3.04(m,2,C_3-H), 3.05(s,3,CH_3), 3.39-3.63(m,2,C_6-H), 5.59(broad s,2,NH_2,exchanges with deuterium oxide), 6.54-7.00(m,2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.29(d($J_{4',5'}$=8Hz) of d($J_{3',4'}$=8Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ phenyl hydrogen), 7.74(d($J_{5',6'}$=8Hz) of d($J_{4',6'}$=2Hz),1,$C_{6'}$ phenyl hydrogen); Exact mass calc'd for $C_{12}H_{17}N_3O_2{}^{32}S$, 267.1041; found (high resolution ms): 267.1043. A sample of CXXXIV did not give an acceptable elemental analysis: Anal. calc'd for $C_{12}H_{17}N_3O_2S$: C, 53.91; H, 6.41; N, 15.72; found: C, 52.45; H, 6.32; N, 14.51.

4.4.1.1.0 1-(2-Phenylethyl)-1,2,3,6-tetrahydropyridine (CXXXV).

1H-1,2,3,6-Tetrahydropyridine (9.0 g, 0.108 mol) and 2-phenylethyl bromide (10.0 g, 0.054 mol) in 75 mL toluene were heated at reflux for 10 h with stirring. The reaction mixture was cooled to 25°C and the precipitate of 1H-1,2,3,6-tetrahydropyridine hydrobromide was filtered. The toluene

was evaporated in vacuo. The residue was distilled from potassium hydroxide pellets at 146°C (21 mm Hg) to give 1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine (CXXXV) (8.8 g, 87%) as a colorless oil: ir(NaCl), 1610 cm^{-1} (C=C); nmr, δ 2.06-2.37(m,2,C_3-H), 2.52-2.90(m,6,C_6-H, $\underline{CH_2CH_2}C_6H_5$), 2.90-3.19(m,2,$C_6$-H), 5.72(m,2,$C_4$-H,$C_5$-H), 7.23(m,5,$C_6H_5$); Exact mass calc'd for $C_{13}H_{17}N$, 187.1361; found: (m + 1) 188 (CI(NH_3)-ms); 105.0705 and 82.0672 (EI-ms).

4.4.1.2.0 1-(2-Phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI).

Freshly sublimed potassium tert-butoxide (0.56 g), anhydrous dimethyl sulfoxide (5.0 mL) and 1-(2-phenylethyl)-1,2,3,6-tetrahydropyridine (4.36 g, 23.3 mmol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was then applied to the contents for 5 min and the nitrogen-vacuum process repeated again. The ampule was then sealed and heated at 90°C for 48 h. The hot contents of the ampule were then added to 4 mL water and quickly extracted with pentane (3 x 25 mL) followed by drying with sodium sulfate. The combined extracts were placed over potassium hydroxide pellets and the pentane removed under a stream of nitrogen to give 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI)(4.06 g, 93%) as a brown liquid: nmr, δ 1.86-2.00

m,2,C_3-H), 2.06-2.17(m,2,C_4-H), 2.49-3.09(m,6,C_2-H, $\underline{CH_2}CH_2C_6H_5$), 5.50-5.93(m,2,$C_5$-H,$C_6$-H), 7.23(m,5,$C_6H_5$); Exact mass calc'd for $C_{13}H_{17}N$: 187.1361; found (high resolution ms): 187.1359.

4.4.2.1.0 1-(2-Phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII).

A solution of 4-chlorobenzenesulfonyl azide (0.60 g, 2.76 mmol) in 10 mL ether was added dropwise to a solution of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) (0.51 g, 2.73 mmol) in 20 mL ether at 25°C with stirring. Evolution of nitrogen gas began 20 sec after final addition of the azide. The reaction was allowed to continue for one hour. The solvent was evaporated *in vacuo* to give a thick oil which was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.46 using 75 mL hot acetone gave 1-(2-phenylethyl)piperidylidene-2-(4-chlorophenyl)sulfonamide (CXXXVII) (0.25 g, 25%) as a white powder: mp, 110-111°C; ir, 1570 cm^{-1} (C=N); nmr,δ 1.52-1.85(m,4,C_4-H,C_5-H), 2.71-3.34 (m,6,C_3-H),C_6H,$\underline{CH_2}CH_2C_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 3.62 (t($J_{CH_2CH_2Ph}$=8Hz),2,$\underline{CH_2}CH_2C_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 6.92-7.33 (m,5,$C_6H_5$), 7.44(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.93(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); *Anal.* calc'd for $C_{19}H_{21}N_2O_2SCl$: C, 60.55; H, 5.62; N, 7.43; found:

C, 60.25; H, 5.66; N, 7.24. Extraction of the band having R_f 0.94 with 75 mL hot acetone gave 4-chlorobenzenesulfonyl azide (0.395 g, 66%) which was identical (nmr and micro tlc) to an authentic sample.

4.4.2.2.0 1-(2-Phenylethyl)piperidylidene-2-(4-aminophenylsulfonamide (CXXXVIII).

A solution of 4-aminobenzenesulfonyl azide (0.48 g, 2.42 mmol) in 10 mL ether was added dropwise to a solution of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) (0.45 g, 2.41 mmol) in 20 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-acetone afforded 1-(2-phenylethyl)piperidylidene-2-(4-aminophenyl)sulfonamide (CXXXVIII)(0.24 g, 29%) as a light yellow powder: mp, 170-171°C; ir, 3370 (NH_2), 3470 (NH_2), 1565 cm^{-1} (C=N); nmr, δ 1.56-1.78(m,4,C_4-H,C_5-H), 2.74-3.28(m,6,C_3-H,C_6-H,$\underline{CH_2}CH_2C_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 3.68 (t($J_{CH_2CH_2Ph}$=8Hz),2,$\underline{CH_2}CH_2CH_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 4.07(broad s,2,$NH_2$,exchanges with deuterium oxide), 6.68(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.00-7.39(m,5,C_6H_5), 7.73(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens). Anal. calc'd for $C_{19}H_{23}N_3O_2S$: C, 63.84; H, 6.49; N, 11.75; found: C, 63.51; H, 6.32; N, 11.47. The filtrate was evaporated in vacuo to give 4-aminobenzenesulfonyl azide (0.295 g, 62%) which was identical (nmr, micro-tlc) to an authentic sample.

4.4.2.3.0 1-(2-Phenylethyl)piperidylidene-2-(3-pyridyl)-sulfonamide (CXXXIX).

A solution of pyridine-3-sulfonyl azide (0.61 g, 3.32 mmol) in 10 mL ether was added dropwise to a solution of 1-(2-phenylethyl)-1,2,3,4-tetrahydropyridine (CXXXVI) (0.62 g, 3.32 mmol) in 15 mL ether with stirring. Evolution of nitrogen gas began 15 sec after addition of the azide. The reaction was allowed to proceed for 1 h. The solvent was evaporated *in vacuo* to give a thick oil which was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.15 with 75 mL hot acetone gave 1-(2-phenylethyl)piperidylidene-2-(3-pyridyl)sulfonamide (CXXXIX)(0.26 g, 23%) as a white solid: mp, 105-106°C; ir, 1575 cm^{-1} (C=N); nmr, δ 1.59-1.87 (m,4,C_4-H,C_5-H), 2.75-3.33(m,6,C_3-H,C_6-H,$\underline{CH_2}CH_2C_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 3.68(t($J_{CH_2CH_2Ph}$=7Hz,2,$\underline{CH_2}CH_2C_6H_5$ or $CH_2\underline{CH_2}C_6H_5$), 6.97-7.60(m,6,$C_6H_5$,$C_5'$ pyridyl proton), 8.31(d($J_{5',6'}$=8Hz) of d($J_{2',6'}$=2Hz) of d($J_{4',6'}$=2Hz),1,C_6' pyridyl hydrogen), 8.82(d($J_{4',5'}$=6Hz) of d($J_{4',6'}$=2Hz),1,C_4' pyridyl hydrogen, 9.29(d($J_{2',6'}$=2Hz),1,C_2' pyridyl hydrogen); Anal. calc'd for $C_{18}H_{21}N_3O_2S$: C, 62.95; H, 6.16, N, 12.23; found: C, 62.52; H, 6.10; N, 12.19. Extraction of the band having R_f 0.82 using 75 mL hot acetone gave pyridine-3-sulfonyl azide (0.41 g, 68%) which was identical (nmr, micro-tlc) to an authentic sample.

4.4.3.1.0 1-[2-(4-Nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXL).

1-(2-Phenylethyl)piperidylidene-2-(4-chlorophenyl)-sulfonamide (CXXXVII)(1.17 g, 3.11 mmol), 3 mL 90% fuming nitric acid and 2 mL nitric acid were stirred vigorously for 4 h at 25°C. The reaction mixture was poured onto 50 mL ice-water and the pH was adjusted to 9 using 1.0 N sodium hydroxide. Extraction with methylene chloride (4 x 50 mL), drying (sodium sulfate) and evaporation of the solvent *in vacuo* gave a thick yellow gum which was subjected to preparative tlc using eighteen 20 x 20 cm silica gel G plates, 0.75 mm in thickness with acetone-ether (1:1 v/v) as the development solvent. Extraction of the band having R_f 0.53 using 60 mL hot acetone gave 0.21 g of an unidentified thick red oil. Extraction of the band having R_f 0.88 using 100 mL hot acetone afforded 1-[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXL)(0.73 g, 61%) as a light yellow solid: mp, 157-158°C; ir, 1350 (NO_2), 1540 (NO_2), 1570 cm $^{-1}$ (C=N); nmr, δ 1.53-2.01(m,4,C_4-H,C_5-H), 2.85-3.52(m,6,C_3-H,C_6-H, $\underline{CH_2}CH_2C_6H_4$-*p*-$NO_2$ or $CH_2\underline{CH_2}C_6H_4$-*p*-$NO_2$), 3.68(t,($J_{CH_2CH_2Ph}$=7Hz),2,$\underline{CH_2}CH_2C_6H_4$-*p*-$NO_2$ or $CH_2\underline{CH_2}C_6H_4$-*p*-$NO_2$), 7.14-7.60(m,4,*ortho* chloro phenyl hydrogens, *ortho* methylene phenyl hydrogens), 7.80-8.22(m,4,*ortho* sulfonyl phenyl hydrogens, *ortho* nitro phenyl hydrogens); *Anal*. calc'd for $C_{19}H_{20}N_3O_4SCl$: C, 54.09; H, 4.78; N, 9.96; found: C, 53.82; H, 4.76; N, 9.82.

4.4.3.2.0 1-[2-(4-Aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)sulfonamide (CXLI).

A solution of 85% hydrazine hydrate (0.5 mL) and 10% palladium on charcoal (30 mg) was added to a suspension of 1-[2-(4-nitrophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)-sulfonamide (CXL)(0.15 g, 0.36 mmol) in 30 mL of 95% ethanol at 0°C with stirring[284]. The reaction was allowed to return to room temperature and stirred for an additional 20 h. The reaction mixture was filtered and 30 mL water added. Extraction with methylene chloride (3 x 30 mL), drying (sodium sulfate) and evaporation of the solvent *in vacuo* afforded 1-[2-(4-aminophenyl)ethyl]piperidylidene-2-(4-chlorophenyl)-sulfonamide (CXLI)(0.095 g, 67%) as a light brown solid: mp, 128-130°C; ir, 3370 (NH_2), 3440 (NH_2) 1575 cm^{-1} (C=N); nmr, δ 1.57-1.88(m,4,C_4-H,C_5-H), 2.75(t($J_{CH_2CH_2Ph}$=7Hz),2, $\underline{CH_2}CH_2C_6H_4$-*p*-$NH_2$ or $CH_2\underline{CH_2}C_6H_4$-*p*-$NH_2$), 2.96-3.40(m,4,$C_3$-H,$C_6$-H), 3.40-3.72(m,4,$\underline{CH_2}CH_2C_6H_4$-*p*-$NH_2$ or $CH_2\underline{CH_2}C_6H_4$-*p*-$NH_2$,$NH_2$, exchanges with deuterium oxide), 6.60(d($J_{2',3'}$=8Hz),2,*ortho* amino phenyl hydrogens), 6.87(d($J_{2',3'}$=8Hz)2,*ortho* methylene phenyl hydrogens, 7.48(d($J_{2'',3''}$=8Hz),2,*ortho* chloro phenyl hydrogens, 7.96(d($J_{2'',3''}$=8Hz),2,*ortho* sulfonyl phenyl hydrogens); Exact mass calc'd for $C_{19}H_{22}N_3O_2{}^{32}S^{35}Cl$: 391.1121; found (high resolution ms): 391.1112; *Anal.* calc'd for $C_{19}H_{22}N_3O_2SCl$: C, 58.23; H, 5.66; found: C, 57.76; H, 5.85.

4.5.1.1.0 1-Cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII).

Cyclopropanecarboxylic acid chloride (3.77 g, 0.036 mol) was added dropwise to a solution of 1H-1,2,3,6-tetrahydropyridine (2.0 g, 0.024 mol) in 20 mL 10% aqueous sodium hydroxide at 0°C with stirring. The reaction was allowed to stir at 0°C for 4 h after which 20 mL water was added. The mixture was extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give a yellow oil which was subjected to chromatography using a neutral Alumina column (11 cm x 2.5 cm). Elution with ether (200 mL) afforded 1-cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII)(2.76 g, 76%) as a colorless oil: ir(NaCl), 1640 cm^{-1} (C=O); nmr, δ 0.68-1.11(m,4,$\overline{\text{CH-}\underline{\text{CH}_2}\text{-}\underline{\text{CH}_2}}$), 1.70-2.37(m,3,$C_3$-H,$\overline{\underline{\text{CH}}\text{-CH}_2\text{-CH}_2}$), 3.56-3.86(m,2,$C_2$-H), 3.88-4.30 (m,2,$C_6$-H), 5.55-6.18(m,2,$C_4$-H,$C_5$-H); Exact mass calc'd for $C_9H_{13}NO$: 151.0997; found (high resolution ms): 151.0999.

4.5.1.2.0 1-Cyclopropylmethyl-1,2,3,6-tetrahydropyridine (CXLIV).

A solution of 1-cyclopropylcarbonyl-1,2,3,6-tetrahydropyridine (CXLIII)(2.0 g, 13.25 mmol) in 10 mL dry ether was added dropwise to a suspension of lithium aluminum hydride (0.90 g) in 60 mL dry ether at 0°C with stirring. When the initial exothermic reaction had subsided, the reaction mixture was refluxed for 12 h. The mixture was then

cooled to 0°C and 5 mL of 20% aqueous sodium hydroxide was added dropwise to destroy any excess lithium aluminum hydride. The inorganic salts were removed by filtration and the ether removed *in vacuo* to afford 1-cyclopropylmethyl-1,2,3,6-tetrahydropyridine (CXLIV)(1.72 g, 95%) as a colorless oil: bp, 174°C (731 mm Hg); ir(NaCl) 1615 $\mathrm{cm^{-1}}$ (C=C); nmr, internal standard-$\mathrm{CH_2Cl_2}$, δ 0.0-1.25(m,5,$\overline{\mathrm{CH{-}CH_2{-}CH_2}}$), 2.09-2.43 (m,4,$\mathrm{C_3}$-H,$\underline{\mathrm{CH_2}}$-$\overline{\mathrm{CH{-}CH_2{-}CH_2}}$), 2.65(m,2,$\mathrm{C_2}$-H), 2.96-3.17(m,2,$\mathrm{C_6}$-H), 5.66-5.92(m,2,$\mathrm{C_4}$-H,$\mathrm{C_5}$-H); Exact mass calc'd for $\mathrm{C_9H_{15}N}$: 137.1205; found (high resolution ms): 137.1204.

4.5.1.3.0 1-Cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV).

Freshly sublimed potassium *tert*-butoxide (0.12 g), anhydrous dimethyl sulfoxide (1.1 mL) and 1-cyclopropylmethyl-1,2,3,6-tetrahydropyridine (CLXIV)(0.70 g, 5.11 mmol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was then applied to the contents for 5 min and the nitrogen-vacuum process repeated. The ampule was sealed under high vacuum and heated at 90°C for 48 h. The hot contents of the ampule were then added to 4 mL water and quickly extracted with pentane (3 x 25 mL) and dried (sodium sulfate). The combined extracts were placed over potassium hydroxide pellets and the pentane removed under a stream of nitrogen to give

1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV)(0.62 g, 89%) as a light brown oil: nmr, internal standard- CH_2Cl_2, δ 0.00-1.23(m,5,$\overline{\underline{\mathrm{CH}}\text{-}\underline{\mathrm{CH_2CH_2}}}$), 1.80-2.14(m,2,$C_3$-H), 2.14-2.43(m,2, $\overline{\underline{\mathrm{CH_2}}\text{-}\mathrm{CH}}\mathrm{CH_2CH_2}$), 2.53-2.79(m,2,$C_4$-H), 2.92-3.14(m,2,$C_2$-H), 5.68-5.80(m,1,$C_5$-H), 5.96(d($J_{5,6}$=8Hz),1,$C_6$-H); Exact mass calc'd for $C_9H_{15}N$: 137.1205; found (high resolution ms): 137.1209.

4.5.2.1.0 1-Cyclobutylcarbonyl-1,2,3,6-tetrahydropyridine (CXLVI).

Cyclobutanecarboxylic acid chloride (7.0 g, 0.059 mmol) was added dropwise to a solution of 1H-1,2,3,6-tetrahydropyridine (3.3 g, 0.040 mol) in 30 mL of 10% aqueous sodium hydroxide at 0°C with stirring. The reaction was stirred at 0°C for 4 h after which 20 mL water was added. The mixture was extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give 1-cyclobutylcarbonyl-1,2,3,6-tetrahydropyridine (CXLVI)(6.6 g, 100%) as a yellow oil: ir(NaCl), 1640 cm^{-1} (C=0); nmr, δ 1.70-2.64(m,8,C_3-H, $\overline{\mathrm{CH}\text{-}\underline{\mathrm{CH_2}}\text{-}\underline{\mathrm{CH_2}}\text{-}\underline{\mathrm{CH_2}}}$), 3.17-4.18(m,5,$C_2$-H,$C_6$-H, $\overline{\underline{\mathrm{CH}}\text{-}\mathrm{CH_2}\text{-}\mathrm{CH_2}\text{-}\mathrm{CH_2}}$), 5.50- 6.08(m,2,$C_4$-H,$C_5$-H); Exact mass calc'd for $C_{10}H_{15}NO$: 165.1153; found (high resolution ms): 165.1152.

4.5.2.2.0 1-Cyclobutylmethyl-1,2,3,6-tetrahydropyridine (CXLVII).

A solution of 1-cyclobutylcarbonyl-1,2,3,6-tetrahydropyridine (CXLVI)(4.0 g, 0.024 mol) in 10 mL dry ether

was added dropwise to a suspension of lithium aluminum hydride (1.92 g) in 75 mL dry ether at 0°C with stirring. When the initial exothermic reaction had subsided the reaction mixture was allowed to reflux for 12 h. The mixture was cooled to 0°C and 8 mL 20% aqueous sodium hydroxide was added dropwise to destroy any excess lithium aluminum hydride. The inorganic salts were removed by filtration and the ether evaporated *in vacuo* to afford 1-cyclobutylmethyl-1,2,3,6-tetrahydropyridine (CXLVII)(3.97 g, 93%) as a light yellow oil: bp, 200-201°C (736 mm Hg); ir (NaCl), 1610 cm^{-1} (C=C); nmr, δ 1.50-2.33(m,8,C_3-H,$\overline{\text{CH-}\underline{\text{CH}_2}\text{-}\underline{\text{CH}_2}\text{-}\underline{\text{CH}_2}}$), 2.33-2.68(m,5,$C_2$-H, $\underline{\text{CH}_2}\text{-}\overline{\underline{\text{CH}}\text{-CH}_2\text{-CH}_2\text{-CH}_2}$), 2.93(m,2,$C_6$-H), 5.44-5.93(m,2,$C_4$-H,$C_5$-H); Exact mass calc'd for $C_{10}H_{17}N$: 151.1361; found (high resolution ms): 151.1356.

4.5.2.3.0 1-Cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII).

Freshly sublimed potassium *tert*-butoxide (0.47 g), anhydrous dimethyl sulfoxide (4.2 mL) and 1-cyclobutylmethyl-1,2,3,6-tetrahydropyridine (CXLVII)(3.0 g, 0.02 mol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was then applied to the contents for 5 min and the nitrogen-vacuum process repeated. The ampule was sealed under high vacuum and heated at 90°C for 48 h. The hot contents of the ampule

were added to 5 mL water and quickly extracted with pentane (3 x 25 mL) followed by drying with sodium sulfate. The combined extracts were placed over potassium hydroxide pellets and the pentane removed under a stream of nitrogen to give 1-cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII)(2.7 g, 90%) as a light brown liquid: nmr, δ 1.40-2.28 (m,8,C_3-H, $\overline{\mathrm{CH\text{-}\underline{CH_2}\text{-}\underline{CH_2}\text{-}\underline{CH_2}}}$), 2.33-3.11(m,7,$C_2$-H,$C_4$-H,$\underline{CH_2}$-$\overline{\mathrm{\underline{CH}\text{-}CH_2\text{-}CH_2\text{-}CH_2}}$), 5.63-5.95(m,2,$C_5$-H,$C_6$-H); Exact mass calc'd for $C_{10}H_{17}N$: 151.1361; found (high resolution ms): 151.1358.

4.5.3.1.0 1-Cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CIL).

A solution of 4-chlorobenzenesulfonyl azide (0.34 g, 1.56 mmol) in 10 mL ether was added dropwise with stirring to a solution of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV)(0.21 g, 1.53 mmol) in 20 mL ether at 25°C. Evolution of nitrogen gas began 10 sec after final addition of the azide. The reaction was allowed to proceed for 1 h. The solvent was removed in vacuo to give 0.50 g of a yellow solid of which an aliquot (0.46 g) was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.37 using 75 mL hot acetone afforded 1-cyclopropylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CIL)(0.26 g, 56%) as a white powder: mp, 114-115°C; ir, 1575 cm^{-1} (C=N); nmr, δ 0.18-1.36(m,5,$\overline{\mathrm{\underline{CH}\text{-}\underline{CH_2}\text{-}\underline{CH_2}}}$), 1.65-2.05(m,4,$C_4$-H,$C_5$-H),

2.96-3.28(m,2,C_3-H), 3.31-3.61(m,4,C_6-H,$\underline{CH_2}$-$\overline{CH-CH_2-CH_2}$), 7.42 (d($J_{2',3'}$=9Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.89(d($J_{2',3'}$=9Hz), 2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); Anal. calc'd for $C_{15}H_{19}N_2O_2SCl$: C, 55.12; H, 5.86; N, 8.57; found: C, 54.90; H, 5.86; N, 8.44. Extraction of the band having R_f 1.0 with 75 mL hot acetone afforded 4-chlorobenzenesulfonyl azide (0.081 g, 26%) which was identical (nmr, micro tlc) with an authentic sample.

4.5.3.2.0 1-Cyclopropylmethylpiperidylidene-2-(4-aminophenyl)-sulfonamide (CL).

A solution of 4-aminobenzenesulfonyl azide (0.935 g, 4.72 mmol) in 10 mL ether was added dropwise to a solution of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV) (0.645 g, 4.71 mmol) in 40 mL ether at 25°C according to General Procedure B. Recrystallization from acetone afforded 1-cyclopropylmethylpiperidylidene-2-(4-aminophenyl)sulfonamide (CL)(0.76 g, 52%) as a white powder: mp, 165°C; ir, 1570 (C=N), 3380 (NH_2) 3465 cm^{-1} (NH_2); nmr, $CDCl_3/DMSO\text{-}d_6$, δ 0.14-1.37(m,5,$\overline{\underline{CH}-\underline{CH_2}-\underline{CH_2}}$), 1.49-2.02(m,4,$C_4$-H,$C_5$-H), 2.68-3.09 (m,2,$C_3$-H), 3.09-3.69(m,4,$C_6$-H,$\underline{CH_2}$-$\overline{CH-CH_2-CH_2}$), 5.32(broad s,2, NH_2,exchanges with deuterium oxide), 6.67(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.52(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); Exact mass calc'd for $C_{15}H_{21}N_3O_2{}^{32}S$: 307.1355; found (high resolution ms): 307.1357; Anal. calc'd for $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89; N, 13.67; found: C, 58.13; H, 6.87; N, 13.19.

4.5.3.3.0 1-Cyclopropylmethylpiperidylidene-2-(3-pyridyl)-sulfonamide (CLI).

A solution of pyridine-3-sulfonyl azide (1.02 g, 5.54 mmol) in 15 mL ether was added dropwise to a solution of 1-cyclopropylmethyl-1,2,3,4-tetrahydropyridine (CXLV)(0.76 g, 5.55 mmol) in 40 mL ether at 25°C with stirring. Evolution of nitrogen gas began 10 sec after final addition of the azide. The reaction was allowed to proceed for 1 h. The solvent was evaporated *in vacuo* to give 1.53 g of a thick yellow oil of which an aliquot (1.22 g) was subjected to chromatography using a neutral Alumina column (10 cm x 10 cm). Elution with ether (300 mL) afforded pyridine-3-sulfonyl azide (0.17 g, 20%) which was identical (nmr, micro tlc) with an authentic sample. Further elution with acetone (400 mL) afforded 1-cyclopropylmethylpiperidylidene-2-(3-pyridyl)sulfonamide (CLI)(0.74 g, 57%): mp, 89°C; ir, 1580 cm^{-1} (C=N); nmr, δ 0.18-1.53(m,5,$\overline{\underline{CH}-\underline{CH_2}-\underline{CH_2}}$), 1.72-2.04(m,4,$C_4$-H,$C_5$-H), 3.00-3.30 (m,2,$C_3$-H), 3.30-3.69(m,4,$C_6$-H,$\underline{CH_2}$-$\overline{CH-CH_2-CH_2}$), 7.48 (d($J_{5',6'}$=8Hz) of d($J_{4',5'}$=6Hz),1,$C_{5'}$ pyridyl hydrogen), 8.26 (d($J_{5',6'}$=8Hz) of d($J_{2',6'}$=2Hz) of d($J_{4',6'}$=2Hz),1,$C_{6'}$ pyridyl hydrogen), 8.75(d($J_{4',5'}$=6Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ pyridyl hydrogen), 9.17(d($J_{2',6'}$=2Hz),1,$C_{2'}$ pyridyl hydrogen); *Anal.* calc'd for $C_{14}H_{19}N_3O_2S$: C, 57.31; H, 6.53; N, 14.32; found: C, 56.94; H, 6.44; N, 13.98.

4.5.4.1.0 1-Cyclobutylmethylpiperidylidene-2-(4-chlorophenyl)-sulfonamide (CLII).

A solution of 4-chlorobenzenesulfonyl azide (0.68 g, 3.13 mmol) in 10 mL ether was added dropwise to a solution of 1-cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII) (0.48 g, 3.13 mmol) in 20 mL ether at 25°C according to General Procedure B. The precipitate was removed by filtration to afford 1-cyclobutylmethylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CLII)(0.53 g) as a white solid. The filtrate was evaporated *in vacuo* to give a yellow gum which was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.44 using 50 mL hot acetone afforded CLII(0.19 g, total yield: 0.72 g, 68%): mp, 113°C; ir, 1575 cm^{-1} (C=N); nmr, δ 1.58-2.10(m,10,C_4-H, C_5-H,$\overline{\text{CH-}\underline{\text{CH}_2}\text{-}\underline{\text{CH}_2}\text{-}\underline{\text{CH}_2}}$), 2.97-3.54(m,5,$C_3$-H,$C_6$-H,$\overline{\underline{\text{CH}}\text{-CH}_2\text{CH}_2\text{CH}_2}$), 3.54(d($J_{CH_2CH}$=8Hz),2,$\underline{\text{CH}_2}$-$\overline{\text{CH-CH}_2\text{CH}_2\text{CH}_2}$), 7.44(d($J_{2',3'}$=9Hz), 2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.91(d($J_{2',3'}$=9Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); Anal. calc'd for $C_{16}H_{21}N_2O_2SCl$: C, 56.38; H, 6.21; N, 8.22; found: C, 56.32; H, 6.35; N, 8.16. Extraction of the band having R_f 0.97 with 50 mL hot acetone afforded 4-chlorobenzenesulfonyl azide (0.037 g, 5%) which was identical (nmr, micro-tlc) with an authentic sample.

4.5.4.2.0 1-Cyclobutylmethylpiperidylidene-2-(4-aminophenyl)-sulfonamide (CLIII).

A solution of 4-aminobenzenesulfonyl azide (0.475 g, 2.40 mmol) in 10 mL ether was added dropwise to a solution of 1-cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII) (0.36 g, 2.36 mmol) in 20 mL ether at 25°C according to General Procedure B. Recrystallization from acetone afforded 1-cyclobutylmethylpiperidylidene-2-(4-aminophenyl)sulfonamide (CLIII)(0.65 g, 86%) as a white powder: mp, 216-217°C; ir, 1565 (C=N), 3380 (NH_2), 3460 cm^{-1} (NH_2); nmr, $CDCl_3/DMSO\text{-}d_6$, δ 1.54-2.08(m,10,C_4-H,C_5-H,$\overbracket{\text{CH-}\underline{\text{CH}_2\text{CH}_2\text{CH}_2}}$), 2.39-3.07(m,3, C_3-H,$\overbracket{\underline{\text{CH}}\text{-CH}_2\text{CH}_2\text{CH}_2}$), 3.22-3.50(m,2,$C_6$-H), 3.60(d($J_{CHCH_2}$=7Hz), 2,$\underline{\text{CH}_2}$-$\overbracket{\text{CH-CH}_2\text{CH}_2\text{CH}_2}$), 5.43(broad s,2,$NH_2$,exchanges with deuterium oxide), 6.78(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.54(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); *Anal.* calc'd for $C_{16}H_{23}N_3O_2S$: C, 59.79; H, 7.21; N, 13.07; found: C, 59.65; H, 7.31;N, 12.96.

4.5.4.3.0. 1-Cyclobutylmethylpiperidylidene-2-(3-pyridyl)-sulfonamide (CLIV).

A solution of pyridine-3-sulfonyl azide (0.42 g, 2.28 mmol) in 10 mL ether was added dropwise to a solution of 1-cyclobutylmethyl-1,2,3,4-tetrahydropyridine (CXLVIII) (0.35 g, 2.28 mmol) in 25 mL ether at 25°C with stirring. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 h after which the solvent was

evaporated *in vacuo* to give a thick oil. Sublimation at high pressure (65°C, 0.1 Torr) afforded 1-cyclobutylmethylpiperidylidene-2-(3-pyridyl)sulfonamide (CLIV)(0.64 g, 91%) as a light brown solid: mp, 56-57°C; ir, 1575 cm^{-1} (C=N); nmr, δ 1.68-2.10(m,10,C_4-H,C_5-H,$\overline{CH\text{-}\underline{CH_2CH_2CH_2}}$), 2.47-2.93(m,1, $\overline{\underline{CH}\text{-}CH_2CH_2CH_2}$), 3.02-3.50(m,4,$C_3$-H,$C_6$-H), 3.56(d($J_{CHCH_2}$=7Hz), 2,$\underline{CH_2}\text{-}\overline{CHCH_2CH_2CH_2}$), 7.41(d($J_{5',6'}$=8Hz) of d($J_{4',5'}$=5Hz),1,$C_{5'}$ pyridyl hydrogen), 8.28(d($J_{5',6'}$=8Hz) of d($J_{2',6'}$=2Hz) of d($J_{4',6'}$=2Hz),1,$C_{6'}$ pyridyl hydrogen), 8.78(d($J_{4',5'}$=5Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ prydiyl hydrogen), 9.20(d($J_{2',6'}$=2Hz),1,$C_{2'}$ pyridyl hydrogen); *Anal.* calc'd for $C_{15}H_{21}N_3O_2S$: C, 58.61; H, 6.89; N, 13.67; found: C, 58.05; H, 6.95; N, 13.51.

4.6.1.1.0 1-*n*-Propyl-1,2,3,6-tetrahydropyridine (CLV).

1-Bromopropane (3.0 g, 0.024 mol) was added slowly to a solution of 1H-1,2,3,6-tetrahydropyridine (4.05 g, 0.049 mol) in 50 mL benzene at 25°C with stirring. The mixture was heated at reflux for 3 h and then cooled to 0°C. The precipitate of 1,2,3,6-tetrahydropyridine hydrobromide was removed by filtration. The filtrate was extracted with cold 10% aqueous hydrochloric acid (3 x 25 mL), and then neutralized to pH9 with cold 20% aqueous sodium hydroxide. Extraction with ether (4 x 50 mL), drying (sodium sulfate) and evaporation of the solvent *in vacuo* at low temperature afforded 1-*n*-propyl-1,2,3,6-tetrahydropyridine (CLV) (2.02 g, 67%) as a light green oil: bp, 147°C (721 mm Hg) (Lit.[286]; bp, 146-148°C, 756 mm Hg).

4.6.1.2.0 1-*n*-Propyl-1,2,3,4-tetrahydropyridine (CLVI).

Freshly sublimed potassium *tert*-butoxide (0.51 g), anhydrous dimethyl sulfoxide (3.3 mL) and 1-*n*-propyl-1,2,3,6-tetrahydropyridine (2.08 g, 0.017 mol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was applied to the contents for 5 min, then the nitrogen-vacuum process repeated. The ampule was then sealed under high vacuum and heated at 90°C for 48 h. The hot contents of the ampule were then added to 5 mL water, quickly extracted with pentane (3 x 25 mL) and dried (sodium sulfate). The combined extracts were placed over potassium hydroxide pellets and the pentane removed under a stream of nitrogen to afford 1-*n*-propyl-1,2,3,4-tetrahydropyridine (CLVI)(1.06 g, 51%) as a brown liquid: nmr, δ 0.92 (t($J_{CH_2CH_3}$=7Hz),3,CH_3), 1.28-2.10(m,4,C_3-H,$\underline{CH_2}$-CH_3), 2.50-3.12(m,6,C_4-H,C_2-H,$\underline{CH_2}CH_2CH_3$), 5.63 (m,1,C_5-H), 5.80(d($J_{5,6}$=8Hz),1,C_6-H); Exact mass calc'd for $C_8H_{15}N$: 125.1204; found (high resolution ms): 125.1207.

4.6.2.1.0 1-Isobutyl-1,2,3,6-tetrahydropyridine (CLVII).

1-Bromo-2-methylpropane (14.0 g, 0.102 mol) was added slowly to a solution of 1H-1,2,3,6-tetrahydropyridine (17.0 g, 0.205 mol) in 100 mL toluene at 25°C with stirring. The mixture was allowed to reflux for 7 h before cooling to 0°C at which time 1,2,3,6-tetrahydropyridine hydrobromide was removed

by filtration. The filtrate was extracted with cold 10% aqueous hydrochloric acid (4 x 30 mL) and then neutralized to pH 9 using cold 20% aqueous sodium hydroxide. The milky solution was extracted with ether (4 x 75 mL), dried (sodium sulfate) and the solvent evaporated _in vacuo_ to afford 1-isobutyl-1,2,3,6-tetrahydropyridine (CLVII)(10.7 g, 75%) as a light green liquid: bp, 162°C (715 mm Hg); ir(NaCl), 1610 cm^{-1} (C=C); nmr, δ 0.89(d(J_{CHCH_3}=7Hz),6,CH-($\underline{CH_3}$)$_2$), 1.70-2.33(m,5,C_2-H,C_3-H,$\underline{CH}$-(CH_3)$_2$), 2.46(d(J_{CH_2CH}=5Hz), 2,N$\underline{CH_2}$CH), 2.85-3.04(m,2,C_6-H), 5.60-5.80(m,2,C_4-H,C_5-H); Exact mass calc'd for $C_9H_{17}N$: 139.1361; found (high resolution ms): 139.1354.

4.6.2.2.0 1-Isobutyl-1,2,3,4-tetrahydropyridine (CLVIII).

Freshly sublimed potassium _tert_-butoxide (0.56 g), anhydrous dimethylsulfoxide (5.0 mL) and 1-isobutyl-1,2,3,6-tetrahydropyridine (CLVII)(3.3 g, 0.024 mol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was applied to the contents for 5 min, then the nitrogen-vacuum process repeated. The ampule was then sealed under high vacuum (0.2 Torr) and heated at 90°C for 48 h. The hot contents of the ampule were then added to 5 mL water, quickly extracted with pentane (3 x 25 mL) and dried (sodium sulfate). The combined extracts were placed over potassium hydroxide

pellets and the pentane removed under a stream of nitrogen to afford 1-isobutyl-1,2,3,4-tetrahydropyridine (CLVIII)(2.22 g, 67%) as a brown liquid: nmr, δ 0.89(d(J_{CHCH_3}=7Hz),6, CH($\underline{CH_3}$)$_2$), 1.50-2.36(m,5,C_3-H,C_4-H,$\underline{CH}$(CH_3)$_2$), 2.61(d(J_{CHCH_2}=6Hz), N$\underline{CH_2}$CH), 2.82-3.08(m,2,C_2-H), 5.65-5.97(m,2,C_5-H,C_6-H); Exact mass calc'd for $C_9H_{17}N$: 139.1361; found (high resolution ms): 139.1358.

4.6.3.1.0 1-*n*-Propylpiperidylidene-2-(3-chlorophenyl)sulfonamide (CLIX).

A solution of 4-chlorobenzenesulfonyl azide (0.47 g, 2.17 mmol) in 10 mL ether was added dropwise to a solution of 1-*n*-propyl-1,2,3,4-tetrahydropyridine (CLVI)(0.27 g, 2.16 mmol) in 20 mL ether at 25°C with stirring. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 h. The ether was evaporated *in vacuo* to yield a thick yellow gum which was subjected to chromatography using a neutral alumina column (12 cm x 2.5 cm). Elution with ether (200 mL) gave 4-chlorobenzenesulfonyl azide (0.12 g, 26%) which was identical (nmr, micro tlc) with an authentic sample. Further elution with acetone (300 mL) afforded 1-*n*-propylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CLIX)(0.46 g, 68%) as a white solid: mp, 107-108°C; ir, 1575 cm^{-1} (C=N); nmr, δ 0.77(t($J_{CH_2CH_3}$=7Hz),3,CH_3), 1.19-1.98(m,6,C_4-H,C_5-H,$\underline{CH_2}CH_3$), 2.86-3.17(m,2,C_3-H), 3.17-3.57(m,4,C_6-H,$\underline{CH_2}CH_2CH_3$), 7.39 (d($J_{2',3'}$=9Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.86(d($J_{2',3'}$=9Hz),

2,C_2' and C_6' phenyl hydrogens); Anal. calc'd for $C_{14}H_{19}N_2O_2SCl$: C, 53.41; H, 6.08; N, 8.90; found: C, 53.61; H, 6.17; N, 8.90.

4.6.3.2.0 1-n-Propylpiperidylidene-2-(4-aminophenyl)sulfonamide(CLX).

A solution of 4-aminobenzenesulfonyl azide (0.59 g, 2.98 mmol) in 10 mL ether was added dropwise to a solution of 1-n-propyl-1,2,3,4-tetrahydropyridine (CLVI)(0.37 g, 2.96 mmol) in 25 mL ether at 25°C according to General Procedure B. Recrystallization from carbon tetrachloride-acetone afforded 1-n-propylpiperidylidene-2-(4-aminophenyl)sulfonamide (CLX)(0.565 g, 65%) as a white powder: mp, 178-179°C; ir, 1575 (C=N), 3380 (NH_2), 3480 cm^{-1} (NH_2); nmr, δ 0.85 (t($J_{CH_2CH_3}$=8Hz),3,CH_3), 1.37-1.93(m,6,C_4-H,C_5-H,$\underline{CH_2}CH_3$), 2.93-3.18(m,2,C_3-H), 3.18-3.57(m,4,C_6-H,$\underline{CH_2}CH_2CH_3$), 4.02(broad s,2,NH_2,exchanges with deuterium oxide), 6.64(d($J_{2',3'}$=9Hz),2,C_3' and C_5' phenyl hydrogens), 7.63(d($J_{2',3'}$=9Hz),2,C_2' and C_6' phenyl hydrogens); Anal. calc'd for $C_{14}H_{21}N_3O_2S$: C, 56.92; H, 7.17; N, 14.22; found: C, 57.04; H, 7.26; N, 14.05.

4.6.3.3.0 1-n-Propylpiperidylidene-2-(3-pyridyl)sulfonamide (CLXI).

A solution of pyridine-3-sulfonyl azide (0.36 g, 1.96 mmol) in 10 mL ether was added dropwise to a solution of 1-n-propyl-1,2,3,4-tetrahydropyridine (CLVI)(0.245 g,

1.96 mmol) in 20 mL ether at 25°C with stirring. Evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 h. The solvent was evaporated in vacuo to give a tan solid (0.54 g) of which an aliquot (0.45 g) was subjected to chromatogaphy using a neutral alumina column (15 cm x 2.5 cm). Elution with methylene chloride-acetone (200 mL, 1:1 v/v) gave pyridine-3-sulfonyl azide (0.07 g, 24%) which was identical (nmr, micro tlc) with an authentic sample. Elution with acetone (300 mL) afforded 1-n-propylpiperidylidene-2-(3-pyridyl)sulfonamide (CLXI)(0.28 g, 64%) as a white powder: mp, 109-110°C; ir, 1560 cm^{-1} (C=N); nmr, δ 0.86 (t($J_{CH_2CH_3}$=7Hz),3,CH_3), 1.34-2.11(m,6,C_4-H,C_5-H,$\underline{CH_2}CH_3$), 3.00-3.26(m,2,C_3-H), 3.26-3.61(m,4,C_6-H,$\underline{CH_2}CH_2CH_3$), 7.40 (d($J_{5',6'}$=8Hz) of d($J_{4',5'}$=5Hz),1,$C_{5'}$ pyridyl hydrogen), 8.23 (d($J_{5',6'}$=8Hz) of d($J_{4',6'}$=2Hz) of d($J_{2',6'}$=2Hz),1,$C_{6'}$ pyridyl hydrogen), 8.75(d($J_{4',5'}$=5Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ pyridyl hydrogen), 9.17(d($J_{2',6'}$=2Hz),1,$C_{2'}$ pyridyl hydrogen); Anal. calc'd for $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14.93; found: C, 55.27; H, 6.84; N, 14.77.

4.6.4.1.0 1-Isobutylpiperidylidene-2-(4-chlorophenyl)sulfonamide(CLXII).

A solution of 4-chlorobenzenesulfonyl chloride (0.43 g, 1.98 mmol) in 10 mL ether was added dropwise to a solution of 1-isobutyl-1,2,3,4-tetrahydropyridine (CLVIII) (0.28 g, 1.99 mmol) in 20 mL ether at 25°C with stirring.

The evolution of nitrogen gas was immediate. The reaction was allowed to proceed for 1 h. The ether was evaporated *in vacuo* to give a thick oil which was subjected to preparative tlc using ten 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.39 with 75 mL hot acetone afforded 1-isobutylpiperidylidene-2-(4-chlorophenyl)sulfonamide (CLXIII)(0.24 g, 37%) as a white solid: mp, 106°C; ir, 1570 cm^{-1} (C=N); nmr, δ 0.83(d(J_{CHCH_3}=7Hz),6,CH($\underline{CH_3}$)$_2$), 1.48-2.23(m,5,C_4-H), 2.91-3.48(m,6,C_3-H,C_6-H,N$\underline{CH_2}$CH), 7.40 (d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.86(d($J_{2',3'}$)=8Hz), 2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); *Anal*. calc'd for $C_{15}H_{21}N_2O_2SCl$: C, 54.78; H, 6.44; N, 8.52; found: C, 54.81; H, 6.49; N, 8.48. Extraction of the band having R_f 0.93 with 75 mL hot acetone afforded 4-chlorobenzenesulfonyl azide (0.11 g, 26%) which was identical (nmr, micro tlc) with an authentic sample.

4.6.4.2.0 1-Isobutylpiperidylidene-2-(4-aminophenyl)sulfonamide(CLXIII).

A solution of 4-aminobenzenesulfonyl azide (0.39 g, 1.97 mmol) in 10 mL ether was added dropwise to a solution of 1-isobutyl-1,2,3,4-tetrahydropyridine (CLVIII)(0.275 g, 1.98 mmol) in 20 mL ether at 25°C according to General Procedure B. The precipitate was removed by filtration to give 1-isobutylpiperidylidene-2-(4-aminophenyl)sulfonamide

(CLXIII)(0.23 g) as a white solid. The filtrate was evaporated *in vacuo* to afford a yellow gum which was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether-acetone (2:1 v/v) as the development solvent. Extraction of the band having R_f 0.31 with 75 mL hot acetone afforded (CLXIII)(0.07 g). Total yield: 0.30 g, 49% : mp, 184-185°C; ir, 1565 (C=N), 3370 (NH_2), 3450 cm^{-1} (NH_2); nmr, δ 0.86(t(J_{CHCH_3}=7Hz),6, (CH($\underline{CH_3}$)$_2$), 1.66-1.85(m,4,C_4-H,C_5-H), 2.10(t(J_{CHCH_2}=7Hz) of q(J_{CHCH_3}=7Hz),1,$\underline{CH}$(CH_3)$_2$), 3.00-3.10(m,2,C_3-H), 3.26-3.38(m,4,C_6-H,N$\underline{CH_2}$-CH), 4.05 (broad s,2,NH_2,exchanges with deuterium oxide), 6.64(d($J_{2',3'}$=8Hz),2,C_3' and C_5' phenyl hydrogens), 7.69(d($J_{2',3'}$=8Hz),2,C_2' and C_6' phenyl hydrogens); *Anal*. calc'd for $C_{15}H_{23}N_3O_2S$: C, 58.22; H, 7.49; N, 13.58; found: C, 58.37; H, 7.63; N, 13.57.

4.6.4.3.0 1-Isobutylpiperidylidene-2-(3-pyridyl)sulfonamide (CLXIV).

A solution of pyridine-3-sulfonyl azide (0.355 g, 1.93 mmol) was added dropwise to a solution of 1-isobutyl-1,2,3,4-tetrahydropyridine (CLVIII)(0.27 g, 1.94 mmol) in 20 mL ether at 25°C with stirring. Evolution of nitrogen gas was immediate. The reaction was allowed to continue for 1 h. The solvent was evaporated *in vacuo* to give a thick oil which was subjected to preparative tlc using ten 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether-acetone

(5:1 v/v) as the development solvent. Extraction of the band having R_f 0.39 with 75 mL hot acetone afforded 1-isobutylpiperidylidene-2-(3-pyridyl)sulfonamide (CLXIV)(0.24 g, 42%) as a white powder: mp, 66-67°C; ir, 1575 cm^{-1} (C=N); nmr, δ 0.83(d(J_{CHCH_3}=6Hz),6,$CH(\underline{CH_3})_2$), 1.68-2.39(m,5, C_4-H,C_5-H,$\underline{CH}(CH_3)_2$), 2.98-3.52(m,6,C_3-H,C_6-H,$N\underline{CH_2}CH$), 7.50 (d($J_{5',6'}$=8Hz) of d($J_{4',5'}$=5Hz),1,$C_{5'}$ pyridyl hydrogen), 8.28 (d($J_{5',6'}$=8Hz) of d($J_{2',6'}$=2Hz) of d($J_{4',6'}$=2Hz),1,$C_{6'}$ pyridyl hydrogen), 8.79(d($J_{4',5'}$=5Hz) of d($J_{4',6'}$=2Hz),1,$C_{4'}$ pyridyl hydrogen), 9.21(d($J_{2',6'}$=2Hz)1,$C_{2'}$ pyridyl hydrogen); Anal. calc'd for $C_{14}H_{21}N_3O_2S$: C, 56.92; H, 7.17; N, 14.22; found: C, 56.57; H, 7.24; N, 13.97.

4.7.1.1.0 1-(2-Propenyl)-1,2,3,6-tetrahydropyridine(CLXVI).

Allyl bromide (14.5 g, 0.12 mol) was added dropwise to a solution of 1H-1,2,3,6-tetrahydropyridine (10.0 g, 0.12 mol) and pyridine (9.5 g, 0.12 mol) in 75 mL ether at 0°C with stirring. The reaction was allowed to proceed for 1.5 h at 0°C after which the precipitate of pyridine hydrobromide was removed by filtration. The ether filtrate was washed with 50 mL water and the aqueous fraction was extracted with ether (2 x 50 mL). The combined ethereal portions were dried (sodium sulfate) and the solvent removed *in vacuo* to afford 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI)(9.2 g, 62%) as a light yellow liquid: bp, 144°C (723 mm); nmr, δ 2.00-2.37(m,2,C_3-H), 2.53(t($J_{2,3}$=6Hz),2,C_2-H), 2.87-3.18

(m,4,N$\underline{CH_2}$CH,C_6-H), 4.98-5.39(m,2,CH=$\underline{CH_2}$), 5.47-6.21(m,3, C_4-H,C_5-H,CH=CH_2); Exact mass calc'd for $C_8H_{13}N$: 123.1048; found (high resoultion ms): 123.1046.

4.7.1.2.0 E-1-(1-Propenyl)-1,2,3,4-tetrahydropyridine (CLXVII).

Freshly sublimed potassium *tert*-butoxide (0.22 g), anhydrous dimethyl sulfoxide (1.9 mL) and 1-(2-propenyl)-1,2,3,6-tetrahydropyridine (CLXVI)(1.1 g, 8.9 mmol) were added in this order to a thoroughly dry 10 mL ampule. The ampule and its contents were frozen at -77°C and then flushed with nitrogen for 5 min. High vacuum (0.2 Torr) was applied to the contents for 5 min, then the nitrogen-vacuum process repeated. The ampule was then sealed under high vacuum and heated at 90°C for 48 h. The hot contents of the ampule were then added to 5 mL water, quickly extracted with pentane (3 x 25 mL) and dried (sodium sulfate). The combined extracts were placed over potassium hydoxide pellets and the pentane removed under a stream of nitrogen to afford *E*-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII)(0.66 g, 60%) as a brown liquid: nmr, δ 1.60(d(J_{CHCH_3}=8Hz)3,CH-$\underline{CH_3}$), 1.72-2.17 (m,4,C_3-H,C_4-H), 3.03-3.30(m,2,C_2-H), 4.03-4.60(m,2,C_5-H, NCH=$\underline{CH}$), 5.82-6.16(m,2,C_6-H,N$\underline{CH}$=CH); Exact mass calc'd for $C_8H_{13}N$: 123.1048; found (high resolution ms): 123.1047.

4.7.2.0.0 E-1-(1-Propenyl)piperidylidene-2-(4-chlorophenyl)-sulfonamide(CLXXIII) and 1-(4-chlorophenyl)-sulfonimine-1,2,3,4-tetrahydropyridine(CLXXIV).

A. Reaction of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII) and one mole of 4-chlorobenzenesulfonyl azide.

A solution of 4-chlorobenzenesulfonyl azide (0.355 g, 1.63 mmol) in 10 mL ether was added dropwise to a solution of E-1-(1-propenyl)-1,2,3,4-tetrahydropyridine (CLXVII)(0.20 g, 1.63 mmol) at 25°C with stirring. Evolution of nitrogen gas began 15 sec after final addition of the azide. The reaction was allowed to proceed for 1 h. The ether was evaporated *in vacuo* to give a thick green oil which was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether-petroleum ether (bp 30-60°C) (4:1 v/v) as development solvent. Extraction of the band having R_f 0.27 with 50 mL hot acetone gave E-1-(1-propenyl)-piperidylidene-2-(4-chlorophenyl)sulfonamide (CLXXIII)(0.22 g, 43%) as a white powder: mp, 106-107°C; ir, 1540 (C=N), 1600 cm^{-1} (C=C); nmr, δ 1.65-2.23(m,7,C_4-H,C_5-H,CH-$\underline{CH_3}$), 3.03-3.32(m,2,C_3-H), 3.32-3.80(m,2,C_6-H), 5.30(d($J_{CH=CH}$=15Hz) of q(J_{CHCH_3}=6Hz),1,$\underline{CH}$-CH_3), 7.32(d($J_{CH=CH}$=15Hz),1, $\underline{CH}$=CH-CH_3), 7.43(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.92(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens); *Anal.* calc'd for $C_{14}H_{17}N_2O_2SCl$: C, 53.75; H, 5.48; N, 8.96; found: C, 53.39; H, 5.49; N, 8.96. Extraction of the band having R_f 0.48 with 50 mL hot acetone gave 1-(4-chlorophenyl)sulfoni-

mine-1,2,3,4-tetrahydropyridine (CLXXIV)(0.092 g, 20%): mp, 55°C; ir, 1600 cm^{-1} (C=N) nmr, δ 1.80-2.31(m,4,C_3-H,C_4-H), 3.58-3.85(m,2,C_2-H), 5.20-5.44(m,1,C_5-H), 6.42(d($J_{5,6}$=9Hz), 1,C_6-H), 7.41(d($J_{2',3'}$=8Hz),2,$C_{3'}$ and $C_{5'}$ phenyl hydrogens), 7.84(d($J_{2',3'}$=8Hz),2,$C_{2'}$ and $C_{6'}$ phenyl hydrogens), 8.24(s,1,CH=N); Exact mass calc'd for $C_{10}H_{13}N_2O_2{}^{32}S^{35}Cl$: 284.0385; found (high resolution ms): 284.0385. A sample of CLXXIV did not give an acceptable elemental analysis. Extraction of the band having R_f 0.85 with 50 mL hot acetone gave 4-chlorobenzenesulfonyl azide (0.018 g, 5%) whose spectra was identical (nmr and micr-tlc) to those of an authentic sample.

B. Reaction of CLXVII with two moles of 4-chlorobenzenesulfonyl azide.

A solution of 4-chlorobenzenesulfonyl azide (0.71 g, 3.26 mmol) in 20 mL ether was added dropwise to a solution of CLXVII (0.20 g, 1.63 mmol) in 20 mL ether at 25°C with stirring. The reaction was completed as described for the preparation of CLXXIII and CLXXIV. The crude reaction product was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether-petroleum ether (bp 30-60°C) (4:1 v/v) as the development solvent. Extraction of the band having R_f 0.28 with 50 mL hot acetone gave CLXXIII (0.22 g, 43%). Extraction of the band having R_f 0.50 with 50 mL hot acetone gave CLXXIV (0.073 g, 16%). Extraction of the band having R_f 0.85 gave 4-chlorobenzenesulfonyl azide (0.29 g, 41%).

4.8.1.0.0 10-(3-Dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]benzothiazine (CXII). General Procedure C.

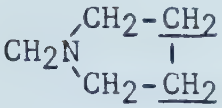
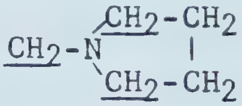
In a dry nitrogen atmosphere 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) was added portionwise with stirring to a suspension of sodium hydride (0.28 g, 11.5 mmol) in anhydrous toluene (80 mL) and anhydrous dioxane (20 mL). The resulting light orange suspension was heated at reflux for one hour, allowed to cool, and 3-dimethylaminopropyl chloride (1.21 g, 10 mmol) was added portionwise over 1 h. The mixture was allowed to reflux for 12 h to give a dark red suspension which was cooled to room temperature and filtered under a nitrogen stream. The filtrate was extracted with 10% hydrochloric acid (5 x 40 mL) and the pH adjusted to 9 with ammonium hydroxide. The yellow aqueous suspension was extracted with methylene chloride (5 x 40 mL), dried (sodium sulfate) and the solvent removed *in vacuo* to give a dark red oil which was chromatographed using a silica gel column (12 cm x 2.5 cm). Elution with chloroform-methanol (10:1 v/v, 350 mL) gave 10-(3-dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]benzothiazine (CXII) as a light orange oil[270] (1.24 g, 87%): nmr δ $1.84(t(J_{1',2'}=7Hz)$ of $t(J_{2',3'}=7Hz), 2, CH_2\underline{CH_2}CH_2)$, $2.21(s, 6, N(CH_3)_2)$, $2.42(t(J_{2',3'}=7Hz), 2, \underline{CH_2}N(CH_3)_2)$, $3.89(t(J_{1',2'}=7Hz), 2, \underline{CH_2}CH_2CH_2N(CH_3)_2)$, $6.69 (d(J_{1,2}=6Hz), 1, C_1\text{-}H)$, $6.78\text{-}7.21(m, 4, C_6\text{-}C_9\text{-}H)$, $8.13(s, 1, C_4\text{-}H)$, $8.22(d(J_{1,2}=6Hz), 1, C_2\text{-}H)$.

4.8.2.0.0 10-(2-Dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]-benzothiazine (CLXXXVI).

2-Dimethylaminoethyl chloride (1.07 g, 10 mmol) was added to a suspension of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) and sodium hydride (0.28 g, 11.5 mmol) in toluene (80 mL) and dioxane (20 mL) according to General Procedure C. The reaction mixture was heated at reflux for 8 h and completed according to General Procedure C to give 10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXVI)(1.06 g, 78%) as a light orange oil: ir (NaCl), 1595 cm^{-1} (C=C); nmr, δ 2.22(s,6,$N(CH_3)_2$), 2.57 (t($J_{CH_2CH_2}$=7Hz),2,$\underline{CH_2}N(CH_3)_2$), 3.86(t($J_{CH_2CH_2}$=7Hz),2,$N^{10}$-$CH_2$), 6.69(d($J_{1,2}$=6Hz),1,$C_1$-H), 6.81-7.08(m,4,$C_6$-$C_9$-H), 8.09 (s,1,$C_4$-H), 8.20(d($J_{1,2}$=6Hz),1,$C_2$-H); Exact mass calc'd for $C_{15}H_{17}N_3S$: 271.1143; found (high resolution ms): 271.1143.

4.8.3.0.0 10-[3-(1-Pyrrolidinyl)propyl]-10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXXVII).

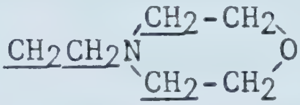
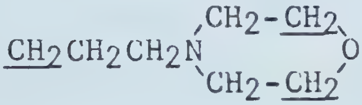
1-Pyrrolidinylpropyl chloride (1.47 g, 10 mmol) in 20 mL of toluene was added to a suspension of 10H-pyrido-[3,4-b][1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) and sodium hydride (0.28 g, 11.5 mmol) in toluene (80 mL) and dioxane (20 mL) according to General Procedure C. The reaction was allowed to proceed for 6 h at reflux. Completion of the reaction according to General Procedure C gave 10-[3-(1-

pyrrolidinyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXVII)(1.13 g, 73%) as a yellow solid: mp, 170-172°C; ir, 1600 cm^{-1} (C=C); nmr, δ 1.78-2.28(m,6,$CH_2\underline{CH_2}CH_2$,  $CH_2N\left\langle\begin{array}{l}CH_2-\underline{CH_2}\\ \qquad\ \ |\\ CH_2-\underline{CH_2}\end{array}\right.$), 2.31-2.82(m,6, $\underline{CH_2}-N\left\langle\begin{array}{l}\underline{CH_2}-CH_2\\ \qquad\ \ |\\ \underline{CH_2}-CH_2\end{array}\right.$), 3.92(t($J_{1,2}$=7Hz), 2,$N^{10}$-$CH_2$, 6.71(d($J_{1,2}$=6Hz),1,$C_1$-H), 6.80-7.19(m,4,$C_6$-$C_9$-H), 8.18(s,1,$C_4$-H), 8.25(d($J_{1,2}$=6Hz),1,$C_2$-H); Exact mass calc'd for $C_{18}H_{21}N_3{}^{32}S$: 311.1456; found (high resolution ms): 311.1451.

4.8.4.0.0 10-[3-(1-Piperidyl)propyl]-10H-pyrido[3,4-b][1,4]-benzothiazine (CLXXXVIII).

1-Piperidylpropyl chloride (1.62 g, 10 mmol) in 20 mL toluene was added to a suspension of 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) and sodium hydride (0.28 g, 11.5 mmol) in toluene (80 mL) and dioxane (20 mL) according to General Procedure C. The reaction mixture was heated at reflux for 6 h and the product isolated according to General Procedure C to yield 10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXVIII)(1.36 g, 84%) as an orange solid: mp, 131-131.5°C; ir, 1605 cm^{-1} (C=C); nmr, δ 1.28-2.78(m,14,$CH_2CH_2N(C_5$-H_{10})), 3.90(t($J_{1',2'}$=7Hz), 2,N^{10}-CH_2), 6.74(d($J_{1,2}$=6Hz),1,C_1-H), 6.83-7.38(m,4,C_6-C_9-H), 8.13(s,1,C_4-H), 8.27(d($J_{1,2}$=6Hz),1,C_2-H); Exact mass calc'd for $C_{19}H_{23}N_3{}^{32}S$: 325.1613; found (high resolution ms): 325.1615.

4.8.5.0.0 10-[3-(4-Morpholino)propyl]-10H-pyrido[3,4-b][1,4]-benzothiazine (CLXXXIX).

4-Morpholinopropyl chloride (1.64 g, 10 mmol) in 20 mL toluene was added to a suspension of 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) and sodium hydride (0.28 g, 11.5 mmol) in toluene (80 mL) and dioxane (20 mL) according to General Procedure C. The reaction mixture was heated at reflux for 8 h. The product was isolated according to General Procedure C to give 10-[3-(4-morpholino)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXIX)(1.44 g, 88%) as an orange solid: mp, 114-115°C; ir, 1590 cm^{-1} (C=C); nmr δ 1.70-2.59(m,8,  $\underline{CH_2CH_2}N\begin{matrix}\underline{CH_2}-CH_2\\ \underline{CH_2}-CH_2\end{matrix}O$), 3.50-4.10 (m,6,  $\underline{CH_2}CH_2CH_2N\begin{matrix}CH_2-\underline{CH_2}\\ CH_2-\underline{CH_2}\end{matrix}O$), 6.70(d($J_{1,2,}$=6Hz),1,$C_1$-H), 6.80-7.21 (m,4,$C_6$-$C_9$-H), 8.18(s,1,$C_4$-H), 8.25(d($J_{1,2}$=6Hz)1,$C_2$-H); Exact mass calc'd for $C_{18}H_{21}N_3O^{32}S$: 327.1405; found (high resolution ms): 327.1404.

4.9.1.1.0 10-(2-Dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]-benzothiazine oxalate (CXC).

Anhydrous oxalic acid (0.35 g, 3.92 mmol) was added to a solution of 10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXXVI)(1.06 g, 3.91 mmol) in absolute ethanol (70 mL). The mixture was heated at reflux for 15 min, cooled to 0°C and filtered to afford 10-(2-dimethyl-

aminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXC)(1.41 g, 100%) as a bright yellow solid: mp, 204-206°C; ir, 1605 (C=C), 1730 cm^{-1} (C=O); nmr, DMSO-d_6, δ 2.79 (s,6,NH($\underline{CH_3}$)$_2$), 3.24(t($J_{CH_2CH_2}$=7Hz),2,N^{10}-$CH_2\underline{CH_2}$), 4.33(t($J_{CH_2CH_2}$=7Hz),2,N^{10}-$\underline{CH_2}CH_2$), 6.43(br s,2,NH, exchanges deuterium oxide,OH,exchanges with deuterium oxide), 7.19(d($J_{1,2}$=6Hz),1,C_1-H), 7.23-7.44(m,4,C_6-C_9-H), 8.27(s,1,C_4-H), 8.38(d($J_{1,2}$=6Hz),1,C_2-H); Anal. calc'd for $C_{17}H_{19}N_3O_4S$: C,56.50; H, 5.30; N, 11.63; found: C,56.12; H, 5.19; N, 11.40.

4.9.1.2.0 3-Methyl-10-(2-dimethylaminoethyl)-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide oxalate (CXCI).

Methyl iodide (0.87 g, 6.1 mmol) was added all at once to a solution of 10-(2-dimethylaminoethyl)-10H-pyrido-[3,4-b][1,4]benzothiazine oxalate (CXC)(1.1 g, 3.05 mmol) at reflux temperature in absolute ethanol (100 mL). The mixture was allowed to reflux for 4 h and the solvent evaporated *in vacuo* to a 25 mL volume. The solution was cooled to 0°C and filtered to give 3-methyl-10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCI) (1.38 g, 90%) as a yellow solid: mp, >250°C; ir, 1590 (C=C), 1740 cm^{-1} (C=O); nmr, DMSO-d_6/D_2O, δ 3.22(s,6,NH($\underline{CH_3}$)$_2$), 3.80(m,2,N^{10}-$CH_2\underline{CH_2}$), 4.08(s,3,N^3-CH_3), 4.50(s,HOD), 4.64 (m,2,N^{10}-$\underline{CH_2}CH_2$), 7.15-7.51(m,5,C_1-H,C_6-C_9-H), 8.29-8.51 (m,2,C_2-H,C_4-H); Anal. calc'd for $C_{18}H_{22}N_3O_4SI$: C, 42.95;

H, 4.41; N, 8.34; found: C, 42.67; H, 4.28; N, 7.94.

4.9.2.1.0 10-(3-Dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]-benzothiazine oxalate (CXCII).

Anhydrous oxalic acid (0.39 g, 4.35 mmol) was added to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,4-b][1,4]benzothiazine (CXII)(1.24 g, 4.35 mmol) in absolute ethanol (75 mL). The mixture was heated at reflux for 10 min, cooled to 0°C, and filtered to afford 10-(3-dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXCII)(1.63 g, 100%) as a bright yellow solid: mp, 146-148°C; ir, 1600 (C=C), 1750 cm^{-1} (C=O). The oxalate salt CXCII was unstable in air and was converted immediately to the methyl iodide (CXCIII).

4.9.2.2.0 3-Methyl-10-(3-dimethylaminopropyl)-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide oxalate (CXCIII).

Methyl iodide (1.10 g, 7.8 mmol) was added all at once to a solution of 10-(3-dimethylaminopropyl)-10H-pyrido-[3,4-b][1,4]benzothiazine oxalate (CXCII)(1.46 g, 3.9 mmol) at reflux temperature in absolute ethanol (150 mL). The solution was allowed to reflux for 4 h and the solvent volume reduced *in vacuo* to 25 mL. The mixture was cooled to 0°C and filtered to give 3-methyl-10-(3-dimethylaminopropyl)-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCIII)

(1.53 g, 76%) as a yellow solid: mp: 189-191°C; ir, 1600 (C=C), 1740 cm^{-1} (C=O); nmr, DMSO-d_6/D_2O, δ 2.15 (m,2,$CH_2\underline{CH_2}CH_2$), 2.80(s,6,NH($\underline{CH_3}$)$_2$), 3.17(m,5,N^3-CH_3, $\underline{CH_2}NH(CH_3)_2$), 4.22(m,3,HOD,$N^{10}\underline{CH_2}CH_2$), 7.08-7.50 (m,5,$C_1$-H,$C_6$-$C_9$-H), 8.20-8.48(m,2,$C_2$-H,$C_4$-H). The salt CLXXXIX was unstable to air and used immediately in the subsequent reduction with sodium borohydride.

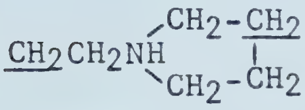
4.9.3.1.0 10-[3-(1-Pyrrolidinyl)propyl]-10H-pyrido[3,4-b]-[1,4]benzothiazine oxalate (CXCIV).

Anhydrous oxalic acid (0.29 g, 3.21 mmol) was added to a solution of 10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazine (CLXXXVII)(1.0 g, 3.21 mmol) in absolute ethanol (40 mL). The mixture was heated at reflux for 15 min, cooled to 0°C, and the solid filtered to afford 10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXCIV)(1.26 g, 98%) as a yellow solid: mp, 129-131°C; ir, 1600 (C=C), 1730 cm^{-1} (C=O). The oxalate salt CXCIV was unstable in air and was converted immediately to the methyl iodide (CXCV).

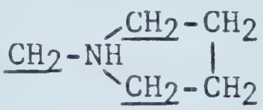
4.9.3.2.0 3-Methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide oxalate (CXCV).

Methyl iodide (0.73 g, 5.2 mmol) was added all at once to a solution of 10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXCIV)(1.0 g,

2.5 mmol) at reflux temperature in absolute ethanol (100 mL). The mixture was allowed to reflux for 4 h and the solvent volume reduced in vacuo to 20 mL. The solution was cooled to 0°C and filtered to yield 3-methyl-10-[3-(1-pyrrolidinyl)-propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCV)(1.22 g, 90%) as a yellow solid: mp, 233-235°C; ir, 1590 (C=C), 1740 cm^{-1} (C=O); nmr, DMSO-d_6, δ 1.94(m,6,



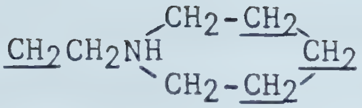
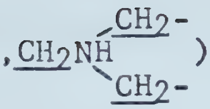
$\underline{CH_2}CH_2NH\begin{array}{l}\diagup CH_2-\underline{CH_2}\\ \qquad\quad |\\ \diagdown CH_2-CH_2\end{array}$), 3.42(m,6,



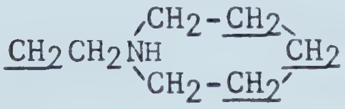
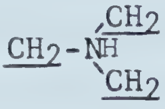
$\underline{CH_2}-NH\begin{array}{l}\diagup \underline{CH_2}-CH_2\\ \qquad\quad |\\ \diagdown \underline{CH_2}-CH_2\end{array}$), 4.06(m,5,$N^3$-$CH_3$,NH, exchanges with deuterium oxide,OH,exchanges with deuterium oxide), 4.70(m,2,$N^{10}CH_2$), 7.27(m,5,C_1-H,C_6-C_9-H), 8.51(m,2, C_2-H,C_4-H). The salt CXCI was unstable in air and was used immediately in the subsequent reduction with sodium borohydride.

4.9.4.1.0 10-[3-(1-Piperidyl)propyl]-10H-pyrido[3,4-b][1,4]-benzothiazine oxalate (CXCVI).

Anhydrous oxalic acid (0.38 g, 4.18 mmol) was added to a solution of 10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXXVIII)(1.36 g, 4.18 mmol) in absolute ethanol (30 mL). The mixture was heated at reflux for 20 min and the solvent removed in vacuo to afford 10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine oxalate (CXCVI)(1.73 g, 100%) as a bright yellow solid: mp, 161-163°C; ir, 1600 (C=C), 1730 cm^{-1} (C=O); nmr, DMSO-d_6 , δ

1.32-2.21(m,8,  $\underline{\mathrm{CH_2}}\mathrm{CH_2NH}\begin{matrix}\diagup\mathrm{CH_2}-\underline{\mathrm{CH_2}}\diagdown\\ \diagdown\mathrm{CH_2}-\underline{\mathrm{CH_2}}\diagup\end{matrix}\underline{\mathrm{CH_2}}$), 2.65-3.22(m,6,  $\underline{\mathrm{CH_2}}\mathrm{N}\underline{\mathrm{H}}\begin{matrix}\diagup\underline{\mathrm{CH_2}}-\\ \diagdown\underline{\mathrm{CH_2}}-\end{matrix}$), 4.00(m,2,$N^{10}-CH_2$), 6.90-7.31(m,5,$C_1$-H,$C_6$-$C_9$-H, 8.16 (s,1,$C_4$-H), 8.32(d($J_{1,2}$=5Hz),1,$C_2$-H). The oxalate salt CXCVI was unstable in air and was converted immediately to the methyl iodide CXCVII.

4.9.4.2.0 3-Methyl-10-[3-(1-piperidyl)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide oxalate (CXCVII).

Methyl iodide (1.04 g, 7.3 mmol) was added all at once to a solution of 10-[3-(1-piperidyl)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazine oxalate (CXCVI)(1.51 g, 3.64 mmol) in absolute ethanol (50 mL) at reflux temperature. The mixture was heated at reflux for 6 h and the solvent removed *in vacuo* to give 3-methyl-10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCVII) (2.03 g, 100%) as a yellow solid: mp, 205-207°C; ir, 1745 cm^{-1} (C=O); nmr, DMSO-d_6/D_2O, δ 1.42-2.50(m,8,  $\underline{\mathrm{CH_2}}\mathrm{CH_2NH}\begin{matrix}\diagup\mathrm{CH_2}-\underline{\mathrm{CH_2}}\diagdown\\ \diagdown\mathrm{CH_2}-\underline{\mathrm{CH_2}}\diagup\end{matrix}\underline{\mathrm{CH_2}}$), 2.50-3.55(m,6,  $\underline{\mathrm{CH_2}}-\mathrm{N}\underline{\mathrm{H}}\begin{matrix}\diagup\underline{\mathrm{CH_2}}\\ \diagdown\underline{\mathrm{CH_2}}\end{matrix}$), 4.00-4.32 (m,5,$NCH_3$,$N^{10}-CH_2$), 4.70(s,HOD), 7.11-7.42(m,5,C_1-H,C_6-C_9-H), 8.17-8.36(m,2,C_2-H,C_4-H). The salt CXCVII was unstable in air and was used immediately in the subsequent reaction with sodium borohydride.

4.9.5.1.0 10-[-3-(4-Morpholino)propyl]-10H-pyrido[3,4-b]-[1,4]benzothiazine oxalate (CXCVIII).

Anhydrous oxalic acid (0.275 g, 3.06 mmol) was added to a solution of 10-[3-(4-morpholino)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXIX)(1.0 g, 3.06 mmol) in absolute ethanol (40 mL). The mixture was heated at reflux for 15 min, cooled at 0°C, and the solid filtered to afford 10-[3-(4-morpholino)propyl]-10H-pyrido[3,4-b][1,4]-benzothiazine oxalate (CXCVIII)(1.23 g, 96%) as a yellow solid: mp, 162-164°C; ir, 1740 cm^{-1} (C=O); nmr, DMSO-d_6, δ 1.81-2.40(m,2,N^{10}-$CH_2\underline{CH_2}$), 2.96-3.38(m,6, $CH_2NH(CH_2)_2$), 3.57-4.16(m,6,N^{10}-$\underline{CH_2}$,CH_2-O-CH_2), 6.90-7.30 (m,5,C_1-H,C_6-C_9-H), 8.12-8.87(m,3,C_2-H,C_4-H,OH,exchanges with deuterium oxide). The oxalate salt CXCVIII was unstable in air and was converted immediately to the methyl iodide CIC.

4.9.5.2.0 3-Methyl-10-[3-(4-morpholino)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide oxalate (CIC).

Methyl iodide (0.68 g, 4.8 mmol) was added all at once to a solution of 10-[3-(4-morpholino)propyl]-10H-pyrido-[3,4-b][1,4]benzothiazine oxalate (CXCVIII)(1.0 g, 2.4 mmol) in absolute ethanol (100 mL) at reflux temperature. The mixture was heated at reflux for 4 h and the solvent reduced *in vacuo* to a 20 mL volume. The mixture was cooled to 0°C and filtered to afford 3-methyl-10-[3-(4-morpholino)-

propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CIC)(1.23 g, 92%) as a yellow solid: mp, 213-215°C; ir, 1640 cm^{-1} (C=O). The salt CXCV was unstable in air and was used immediately in the subsequent reaction with sodium borohydride.

4.10.1.1.0 3-Methyl-10-(2-dimethylaminoethyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CC).

Sodium borohydride (0.91 g, 23.9 mmol) was added slowly to a suspension of 3-methyl-10-(2-dimethylaminoethyl)-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCI) (1.20 g, 2.39 mmol) in 95% ethanol (35 mL) at 0°C with stirring. The mixture was allowed to stir for 20 min at 0°C at which time all the color had dissipated. The suspension was poured onto ice-water (75 mL), extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to afford 3-methyl-10-(2-dimethylaminoethyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CC)(0.425 g, 61%) as a light green oil. A sample suitable for analysis was obtained by preparative tlc using silica gel G plates with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.29 gave CC: ir (NaCl); 1590 cm^{-1} (C=C); nmr, δ 2.08-4.41(m,19,NCH_3,$CH_2CH_2N(CH_3)_2$,C_1-H,C_2-H,C_4-H), 6.69-7.47 (m,4,C_6-C_9-H); Exact mass calc'd for $C_{16}H_{23}N_3{}^{32}S$: 289.1616; found (high resolution ms): 289.1607; *Anal*. calc'd for $C_{16}H_{23}N_3S$: C, 66.40; H, 8.01; N, 14.52; found:

C, 65.58; H, 7.83; N, 14.37.

4.10.1.2.0 3-Methyl-10-(2-dimethylaminoethyl)-10H-1,1a,2,3-4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCII).

10% Palladium on charcoal (200 mg) was added to a solution of 3-methyl-10-(2-dimethylaminoethyl)-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CC)(0.47 g, 1.63 mmol) in 95% ethanol (30 mL). The mixture was hydrogenated at 25°C for 24 h using hydrogen gas at 35 psi. The palladium-charcoal was filtered and the solvent evaporated *in vacuo* to give a red oil (0.55 g) which was subjected to purification on a basic Alumina column (8 cm x 2.5 cm) using chloroform-methanol (15:1 v/v). The first 140 mL fraction was discarded. The next 100 mL fraction afforded 3-methyl-10-(2-dimethylaminoethyl)-10H-1,1a,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCII)(0.18 g, 38%) as a light green oil: ir (NaCl), 1600 cm^{-1} (C=C); nmr $CDCl_3/DMSO-d_6$, δ 2.2-4.5(m,21,C_1-H,C_{1a}-H,C_2-H,C_4-H,C_{4a}-H, NCH_3,$CH_2CH_2N(CH_3)_2$), 6.7-7.32(m,4,C_6-C_9-H); Exact mass calc'd for $C_{16}H_{25}N_3{}^{32}S$: 291.1773; found (high resolution ms): 291.1771.

4.10.2.1.0 3-Methyl-10-(3-dimethylaminopropyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCIII).

Sodium borohydride (0.735 g, 19.3 mmol) was added slowly to a suspension of 3-methyl-10-(3-dimethylaminopropyl)-

10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCIII) (1.0 g, 1.93 mmol) in 95% ethanol (30 mL) at 0°C with stirring. The reaction was allowed to proceed with stirring for 30 min at which time all color had dissipated. The suspension was poured onto ice-water (75 mL), extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to afford 3-methyl-10-(3-dimethylaminopropyl)-10H-1,2,3,4-tetrahydropyrido[3,4-b]-[1,4]benzothiazine (CCIII) as a light green oil (0.33 g, 57 %). A sample suitable for analysis was obtained by preparative tlc using silica gel G plates, 20 x 20 cm, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.26 gave CCIII: ir (NaCl), 1595 cm^{-1} (C=C); nmr, δ 1.58-2.61(m,17,NCH_3,$CH_2CH_2N(CH_3)_2$,C_1-H,C_2-H), 2.77-3.97 (m,4,C_4-H,N^{10}-CH_2), 6.50-7.27(m,4,C_6-C_9-H); Exact mass calc'd for $C_{17}H_{25}N_3{}^{32}S$: 303.1769; found (high resolution ms): 303.1780; *Anal*. calc'd for $C_{17}H_{25}N_3S$: C, 67.28; H, 8.30; N, 13.85; found: C, 67.96; H, 8.40; N, 14.08.

4.10.2.2.0 *3-Methyl-10-(3-dimethylaminopropyl)-10H-1,1a,2-3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCIV)*.

10% Palladium on charcoal (200 mg) was added to a solution of 3-methyl-10-(3-dimethylaminopropyl)-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCIII)(0.59 g,

1.95 mmol) in 95% ethanol (30 mL). The mixture was hydrogenated at 25°C for 24 h using hydrogen gas at 35 psi. The palladium-charcoal was filtered and the solvent evaporated in vacuo to give a red oil (0.56 g) which was subjected to purification on a basic Alumina column (10 cm x 2.5 cm). Elution with 150 mL chloroform-methanol (15:1 v/v) afforded 3-methyl-10-(3-dimethylaminopropyl)-10H-1,1a,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCIV) as a thick green oil (0.22 g, 37%): ir (NaCl), 1595 cm^{-1} (C=C); nmr, δ $CDCl_3/DMSO-d_6$, 1.72-4.26(m,23,NCH_3,$CH_2CH_2CH_2N(CH_3)_2$, C_{1a}-H,C_1-H,C_2-H,C_4-H,C_{4a}-H), 6.63-7.34(m,4,C_6-C_9-H); Exact mass calc'd for $C_{17}H_{27}N_3{}^{32}S$: 305.1926; found: (high resolution ms): 305.1916.

4.10.3.1.0 3-Methyl-10-[3-(1-piperidyl)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCV).

Sodium borohydride (0.61 g, 16.1 mmol) was added slowly to a suspension of 3-methyl-10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCVII) (0.89 g, 1.60 mmol) in 95% ethanol (40 mL) at 0°C with stirring. The mixture was allowed to stir for a further 20 min at 0°C at which time the yellow color had dissipated. The suspension was poured onto ice-water (75 mL), extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated in vacuo to give a light red oil (0.53 g). A portion of this oil (0.27 g) was subjected to

preparative tlc using six 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.30 using 45 mL hot methanol afforded 3-methyl-10-[3-(1-piperidyl)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b]-[1,4]benzothiazine (CCV)(0.057 g, 22%) as a green oil: ir (NaCl), 1590 cm^{-1} (C=C); nmr, δ 1.27-2.77(m,21,NCH_3, $CH_2CH_2N(C_5H_{10})$,C_1-H,C_2-H), 2.83-2.97(m,4,N^{10}-CH_2,C_4-H), 6.62-7.30(m,4,C_6-C_9-H); Exact mass calc'd for $C_{20}H_{29}N_3{}^{32}S$: 343.2082; found (high resolution ms): 343.2078; *Anal*. calc'd for $C_{20}H_{29}N_3S$: C, 69.93; H, 8.51; N, 12.23; found: C, 69.59; H, 8.27; N, 11.82. Extraction of the band having R_f 0.69 using 40 mL hot methanol afforded 10-[3-(1-piperidyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVIII)(0.051 g, 20%) which was identical (nmr and micro-tlc) to an authentic sample.

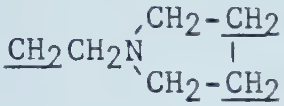
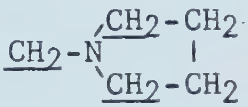
4.10.3.2.0 3-Methyl-10-[3-(1-piperidyl)propyl]-10H-1,1a,2,3-4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCVI).

10% Palladium on charcoal (200 mg) was added to a solution of 3-methyl-10-[3-(1-piperidyl)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCV)(0.66 g, 1.92 mmol) in 95% ethanol (35 mL). The mixture was hydrogenated at 25°C for 24 h using hydrogen gas at 35 psi. The palladium-charcoal was filtered and the solvent evaporated

in vacuo to give a red gum (0.61 g). The gum was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.26 with 50 mL hot methanol afforded 3-methyl-10-[3-(1-piperidyl)propyl]-10H-1,1a,2,3-4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCVI) as a light red gum (0.225 g, 34%): ir, 1590 cm^{-1} (C=C); nmr, $CDCl_3/DMSO-d_6$, δ 1.23-4.81(m,27,NCH_3,$CH_2CH_2CH_2N(C_5H_{10})$, C_{1a}-H,C_1-H,C_2-H,C_4-H,C_{4a}-H), 6.69-7.42(m,4,C_6-C_9-H); Exact mass calc'd for $C_{20}H_{31}N_3{}^{32}S$: 345.2238; found (high resolution ms): 345.2238.

4.10.4.1.0 3-Methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCVII).

Sodium borohydride (0.38 g, 10.1 mmol) was added slowly with stirring to a suspension of 3-methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CXCV)(0.58 g, 1.07 mmol) in 95% ethanol (25 mL) at 0°C. The reduction was allowed to proceed for 25 min at 0°C at which time the color had dissipated. The suspension was poured onto ice-water (50 mL), extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give a thick red oil (0.36 g). A portion of this oil (0.28 g) was subjected to

preparative tlc using six 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.33 using 50 mL hot methanol gave 3-methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-1,2,3,4-tetrahydropyrido-[3,4-b][1,4]benzothiazine (CCVII)(0.058 g, 21%) as a light green oil: ir (NaCl), 1595 cm^{-1} (C=C); nmr, δ 1.63-2.17 (m,6,$\underline{CH_2}CH_2N\begin{array}{l}\diagup CH_2\text{-}\underline{CH_2}\\ \quad\quad\; | \\ \diagdown CH_2\text{-}\underline{CH_2}\end{array}$), 2.17-2.82(m,13,$NCH_3$,$\underline{CH_2}\text{-}N\begin{array}{l}\diagup \underline{CH_2}\text{-}CH_2\\ \quad\quad\; | \\ \diagdown \underline{CH_2}\text{-}CH_2\end{array}$,$C_1$-H, C_2-H), 3.02(m,2,C_4-H), 3.29-4.40(m,2,N^{10}-CH_2), 6.56-7.37 (m,4,C_6-C_9-H); Exact mass calc'd for $C_{19}H_{27}N_3S$: 329.1926; found (high resolution ms): 329.1924; Anal. calc'd for $C_{19}H_{27}N_3S$: C, 69.26; H, 8.26; N, 12.75; found: C, 69.01; H, 8.31; N, 12.50. Extraction of the band having R_f 0.72 with 50 mL hot methanol gave 10-[3-(1-pyrrolidinyl)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXVII)(0.047 g, 18%) which was identical (nmr and micro-tlc) to an authentic sample.

4.10.4.2.0 3-Methyl-10-[3-[(1-pyrrolidinyl)propyl]-10H-1,1a-2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCVIII).

10% Palladium on charcoal (230 mg) was added to a solution of 3-methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-

1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCVII) (0.87 g, 2.61 mmol) in 95% ethanol (40 mL). The mixture was hydrogenated at 25°C for 24 h using hydrogen gas at 35 psi. The palladium-charcoal was filtered and the solvent evaporated *in vacuo* to give a red gum (0.715 g). The gum was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.28 using 50 mL hot methanol afforded 3-methyl-10-[3-(1-pyrrolidinyl)propyl]-10H-1,1a,2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCVIII) as a light red gum (0.25 g, 29%): ir (NaCl), 1595 cm^{-1} (C=C); nmr, $CDCl_3/DMSO-d_6$, δ 1.53-4.38 (m,25,NCH_3,$CH_2CH_2CH_2N(C_4H_8)$,C_{1a}-H,C_1-H,C_2-H,C_4-H, C_{4a}-H), 6.55-7.32(m,4,C_6-C_9-H); Exact mass calc'd for $C_{19}H_{29}N_3{}^{32}S$: 331.2082; found (high resolution ms): 331.2074.

4.10.5.1.0 3-Methyl-10-[3-(4-morpholino)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCIX).

Sodium borohydride (0.54 g, 14.3 mmol) was added slowly to a suspension of 3-methyl-10-[3-(4-morpholino)-propyl]-10H-pyrido[3,4-b][1,4]benzothiazinium iodide oxalate (CIC)(0.80 g, 1.43 mmol) in 95% ethanol (25 mL) at 0°C with stirring. The reaction was allowed to proceed for 30 min at which time the yellow color had dissipated. The

suspension was poured onto ice-water (50 mL), extracted with methylene chloride (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give a red oil (0.535 g). A portion of this oil (0.365 g) was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (3:1 v/v) as the development solvent. Extraction of the band having R_f 0.37 using 50 mL hot methanol afforded 3-methyl-10-[3-(4-morpholino)propyl]-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCIX)(0.068 g, 20%) as a green oil: ir (NaCl), 1590 cm^{-1} (C=C); nmr, δ 1.57-2.09(m,2,$CH_2\underline{CH_2}CH_2$), 2.21-2.77(m,13,NCH_3,$CH_2N(CH_2)_2$, C_1-H,C_2-H), 2.94-3.10(m,2,C_4-H), 3.52-3.91(m,6,N^{10}-CH_2, CH_2OCH_2), 6.69-7.37(m,4,C_6-C_9-H); Exact mass calc'd for $C_{17}H_{27}N_3O^{32}S$: 345.1875; found (high resolution ms): 345.1872; *Anal.* calc'd for $C_{17}H_{27}N_3OS$: C, 66.05; H, 7.88; N, 12.16; found: C, 65.71; H, 7.70; N, 12.08. Extraction of the band having R_f 0.77 using 50 mL hot methanol gave 10-[3-(4-morpholino)propyl]-10H-pyrido[3,4-b][1,4]benzothiazine (CLXXXIX)(0.094 g, 29%) which was identical (nmr and micro-tlc) to an authentic sample.

4.10.5.2.0 3-Methyl-10-[3-(4-morpholino)propyl]-10H-1,1a-2,3,4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCX).

10% Palladium on charcoal (210 mg) was added to a solution of 3-methyl-10-[3-(4-morpholino)propyl]-10H-

1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCIX) (0.71 g, 2.05 mmol) in 95% ethanol (40 mL). The mixture was hydrogenated at 25°C for 24 h using hydrogen gas at 35 psi. The palladium-charcoal was filtered and the solvent evaporated *in vacuo* to give a red gum (0.68 g). The gum was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-methanol (2:1 v/v) as the development solvent. Extraction of the band having R_f 0.42 using 50 mL hot methanol afforded 3-methyl-10-[3-(4-morpholino)propyl]-10H-1,1a,2,3-4,4a-hexahydropyrido[3,4-b][1,4]benzothiazine (CCX)(0.21 g, 30%) as a light red gum: ir(NaCl); 1590 cm^{-1} (C=C); nmr, $CDCl_3/DMSO-d_6$, δ 1.49-4.53(m,25,NCH_3,$CH_2CH_2CH_2C_4H_8O$,C_{1a}-H, C_1-H,C_2-H,C_4-H,C_{4a}-H); 6.63-7.40(m,4,C_6-C_9-H); Exact mass calc'd for $C_{19}H_{29}N_3O^{32}S$: 347.2031; found: (high resolution ms): 347.2023.

4.11.1.1.0 10-Methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXI).

10H-Pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(1.5 g, 7.5 mmol) was added portionwise to a suspension of sodium hydride (0.40 g, 16.5 mmol) in anhydrous tetrahydrofuran (60 mL) under a nitrogen atmosphere at 25°C with stirring. The resulting dark brown suspension was stirred at room temperature for 1 h and methyl iodide (2.34 g, 16.5 mmol) was added dropwise. The suspension was stirred for an

additional hour and the yellowish suspension filtered under a nitrogen stream. The filtrate was treated with water (50 mL), extracted with ether (4 x 50 mL), dried (sodium sulfate) and the solvent removed *in vacuo* to give a red gum. Recrystallization from hexanes gave 10-methyl-10H-pyrido-[3,4-b][1,4]benzothiazine (CCXI)(1.03 g, 64%) as an orange solid: mp, 94-96°C; ir, 1595 cm^{-1} (C=C); nmr, δ 3.35 (s,3,CH_3), 6.63(d($J_{1,2}$=6Hz),1,C_1-H), 6.72-7.39(m,4,C_6-C_9-H), 8.20(s,1,C_4-H), 8.31(d($J_{1,2}$=6Hz),1,C_2-H); Exact mass calc'd for $C_{12}H_{10}N_2{}^{32}S$: 214.0565; found (high resolution ms): 214.0562.

4.11.1.2.0 10-Acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII).

Sodium acetate (0.115 g, 1.40 mmol), acetic anhydride (7.5 mL) and 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(1.0 g, 5 mmol) were heated at reflux for 30 min. The mixture was poured onto 30 mL ice-water and ammonium hydroxide (15 mL) added. The resulting solid was collected by vacuum filtration and recrystallized from hexanes-chloroform to give 10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII)(1.03 g, 85%) as rust plates: mp, 140°C; ir, 1680 cm^{-1} (C=O); nmr, δ 2.29(s,3,CH_3), 7.20-7.50(m,4,C_6-C_9-H), 7.58(d($J_{1,2}$=6Hz),1,C_1-H), 8.57-8.71(m,2,C_2-H,C_4-H); Exact mass calc'd for $C_{13}H_{10}N_2O^{32}S$: 242.0514; found (high resolution ms): 242.0512.

4.11.2.1.0 3,10-Dimethyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide (CCXIII).

10-Methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXI)(0.45 g, 2.1 mmol) and methyl iodide (2.25 g, 15.8 mmol) in 60 mL acetone were heated at reflux for 1 h. The mixture was cooled to 0°C and the yellow solid collected by vacuum filtration to give 3,10-dimethyl-10H-pyrido[3,4-b]-[1,4]benzothiazinium iodide (CCXIII)(0.56 g, 75%): mp, 189-191°C (mp reported[270]: 189-192°C).

4.11.2.2.0 3-Methyl-10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide (CCXIV).

10-Acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII)(0.56 g, 2.33 mmol) and methyl iodide (2.5 g, 17.5 mmol) in 60 mL acetone were heated at reflux for 4 h. The mixture was cooled to 0°C and the yellow solid collected by vacuum filtration to afford 3-methyl-10-acetyl-10H-pyrido-[3,4-b][1,4]benzothiazinium iodide (CCXIV)(0.79 g, 89%): mp, 193-195°C; ir, 1700 cm^{-1} (C=O); nmr, $CD_3OD/DMSO-d_6$, δ 2.40(s,3,$COCH_3$), 4.41(s,3,N^3-CH_3), 7.40-7.77(m,4,C_6-C_9-H), 8.37(d($J_{1,2}$=6Hz),1,C_1-H), 8.96(d($J_{1,2}$=6Hz),1,C_2-H), 9.20 (s,1,C_4-H). This sample was subjected immediately to reduction using sodium borohydride.

4.11.3.1.0 3,10-Dimethyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCXV).

Sodium borohydride (0.22 g, 5.8 mmol) was added portionwise to a suspension of 3,10-dimethyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide (CCXIII)(0.41 g, 1.15 mmol) in 95% ethanol (100 mL) at 0°C with stirring. The reaction was allowed to proceed at 0°C for 2 h and then poured onto 50 mL crushed ice. The mixture was extracted with chloroform (4 x 50 mL), dried (sodium sulfate) and the solvent evaporated in vacuo to afford 3,10-dimethyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCXV)(0.24 g, 96%) as a light green oil: ir (NaCl), 1610 cm^{-1} (C=C); nmr, δ 2.16-2.65(m,5,N^3-CH_3,C_1-H), 2.87-3.13(m,7,N^{10}-CH_3, C_2-H,C_4-H), 6.54-7.30(m,4,C_6-C_9-H); Exact mass calc'd for $C_{13}H_{16}N_2{}^{32}S$: 232.1035; found (high resolution ms): 232.1037.

4.11.3.2.0 3-Methyl-10-acetyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCXVI).

Sodium borohydride (0.19 g, 5.0 mmol) was added portionwise to a suspension of 3-methyl-10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazinium iodide (CCXIV)(0.38 g, 1.0 mmol) in 20 mL methanol at -65°C with stirring. The reaction was allowed to proceed for 1 h at -65°C and then poured onto 50 mL crushed ice. The mixture was extracted with chloroform (4 x 75 mL), dried (sodium sulfate) and the solvent removed

in vacuo to yield 3-methyl-10-acetyl-10H-1,2,3,4-tetrahydropyrido[3,4-b][1,4]benzothiazine (CCXVI)(0.23 g, 88%) as a red oil: ir (NaCl), 1680 cm^{-1} (C=O); nmr, δ 2.11(s,3,$COCH_3$), 2.14-2.96(m,7,NCH_3,C_1-H,C_2-H), 3.04-3.30(m,2,C_4-H); 7.11-7.50(m,4,C_6-C_9-H); Exact mass calc'd for $C_{14}H_{16}N_2O^{32}S$: 260.0983; found (high resolution ms): 260.0985.

4.12.0.0.0 4-Deutero-10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVII) and 4-*n*-butyl-10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXVIII).

n-Butyllithium (0.94 mmol, 0.60 mL of a 1.55 M solution in hexane) was added dropwise to a solution of 10-methyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXI)(0.10 g, 0.47 mmol) in 10 mL anhydrous tetrahydrofuran under a nitrogen atmosphere at 0°C with stirring. The brown solution was allowed to stir for 1 h at 0°C and then allowed to warm to room temperature over a 3 h period. The solution was treated with deuterium oxide (0.2 mL), dried (sodium sulfate) and the solvent removed *in vacuo* to give a light red oil. The oil was subjected to preparative tlc using three 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with methylene chloride-acetone (7:1 v/v) as the development solvent. Extraction of the band having R_f 0.37 using 20 mL hot chloroform afforded 4-deutero-10-methyl-10H-pyrido[3,4-b]-[1,4]benzothiazine (CCXVII)(0.025 g, 25%) as a red semi-solid: nmr, δ 3.36(s,3,CH_3), 6.65(d($J_{1,2}$=6Hz),1,C_1-H),

6.72-7.33(m,4,C_6-C_9-H), 8.27(m,1,C_2-H); Exact mass calc'd for $C_{12}H_9DN_2{}^{32}S$: 215.0626; found (high resolution ms): 215.0617. Extraction of the band having R_f 0.42 using 20 mL hot chloroform gave 4-n-butyl-10-methyl-10H-pyrido-[3,4-b][1,4]benzothiazine (CCXVIII)(0.023 g, 18%) as a red oil: ir (NaCl), 1595 cm^{-1} (C=C); nmr, δ 0.91-2.13(m,7,C_3H_7), 2.72-3.04(m,2,$\underline{CH_2}C_3H_7$), 3.37(s,3,CH_3), 6.53(d($J_{1,2}$=6Hz), 1,C_1-H), 6.70-7.32(m,4,C_6-C_9-H), 8.26(d($J_{1,2}$=6Hz),1,C_2-H); Exact mass calc'd for $C_{16}H_{18}N_2{}^{32}S$: 270.1191; found (high resolution ms): 270.1196.

4.13.0.0.0 10-Methoxycarbonyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXXI) and bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido[3,4-b][1,4]benzothiazine (CCXXII).

A. Reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with diisobutylaluminum hydride and methyl chloroformate.

Diisobutylaluminum hydride (1.73 mmol, 1.73 mL of a 1.0 M solution in hexane) was added dropwise to a suspension of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(0.32 g, 1.6 mmol) in anhydrous tetrahydrofuran (30 mL) under a nitrogen atmosphere at 0°C with stirring. The red solution was stirred for 1 h at 0°C and methyl chloroformate (0.49 g, 5.2 mmol) was added all at once. The resulting red suspension was stirred for 18 h at room temperature under a positive nitrogen pressure. Water (2 mL) was added

and the reaction mixture was allowed to stir for an additional 20 min. A further 10 mL of water was added and the pH of the mixture was adjusted to 10 using 1.0 N sodium hydroxide. The aqueous mixture was extracted with methylene chloride (5 x 40 mL), dried (sodium sulfate) and the solvent evaporated in vacuo to give a thick orange oil which was subjected to preparative tlc using eight 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.35 with 50 mL hot acetone gave 10-methoxycarbonyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXXI) as a yellow solid (0.035 g, 9%): mp, 112-114°C; ir, 1735 cm^{-1} (C=O); nmr, δ 3.86(s,3,CH_3), 7.14-7.70(m,5,C_1-H,C_6-C_9-H), 8.39-8.71 (m,2,C_2-H,C_4-H); Exact mass calc'd for $C_{13}H_{10}N_2O_2{}^{32}S$: 258.0463; found (high resolution ms): 258.0461. Extraction of the band having R_f 0.76 using 50 mL hot acetone afforded bis-(3,10-methoxycarbonyl)-10H-3,4-dihydropyrido-[3,4-b][1,4]benzothiazine (CCXXII)(0.13 g, 25%) as a yellow solid: mp, 142-144°C; ir, 1730 cm^{-1} (C=O); nmr, δ 3.82 (m,6,CH_3), 4.53(m,2,C_4-H), 5.47(d($J_{1,2}$=8Hz),1,C_1-H), 6.83 (m,1,C_2-H), 7.16-7.67(m,4,C_6-C_9-H); Exact mass calc'd for $C_{15}H_{14}N_2O_2{}^{32}S$: 318.0674; found (high resolution ms): 318.0670.

B. Reaction of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) with borane-tetrahydrofuran, sodium bis-(2-methoxyethoxy)-aluminum hydride and methyl chloroformate.

Borane-tetrahydrofuran (1.50 mmol, 1.55 mL of a 0.97 M solution) was added dropwise to a suspension of 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI)(0.30 g, 1.5 mmol) in anhydrous tetrahydrofuran (20 mL) under a nitrogen atmosphere at -78°C with stirring. The temperature was maintained at -78°C for 15 min and then sodium bis-(2-methoxyethoxy)aluminum hydride (3.0 mmol, 0.42 mL of a 70% solution in toluene) was added dropwise, followed by methyl chloroformate (1.71 g, 18.0 mmol) all at once 1 h later. The red suspension was allowed to stir for 16 h at room temperature under a positive nitrogen pressure after which time water (5 mL) was added and stirring continued for an additional 30 min. A further 10 mL of water was added and the pH of the mixture adjusted to 10 using 1.0 N sodium hydroxide. The aqueous mixture was extracted with methylene chloride (5 x 40 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give a red gum. The gum was subjected to preparative tlc using twelve 20 x 20 cm silica gel G plates, 0.75 mm in thickness, with ether as the development solvent. Extraction of the band having R_f 0.36 using 50 mL hot acetone gave CCXXI (0.017 g, 4%) which was identical (nmr and micro-tlc) to an authentic sample described previously. Extraction of the band having R_f 0.76

using 50 mL hot acetone afforded CCXXII (0.18 g, 38%) which was identical (nmr and micro-tlc) to an authentic sample described previously.

4.14.0.0.0 3-*tert*-Butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV).

In a dry nitrogen atmosphere 10H-pyrido[3,4-b]-[1,4]benzothiazine (CLXXVI)(0.30 g, 1.5 mmol) was added portionwise with stirring to a suspension of sodium hydride (0.10 g, 4.2 mmol) in anhydrous tetrahydrofuran (40 mL). The light orange suspension was stirred for 1 h at room temperature and *tert*-butoxycarbonyl azide (0.715 g, 5 mmol) was added dropwise. The red suspension was filtered under a nitrogen stream after stirring for 1 h. Water (20 mL) was added and the mixture extracted with methylene chloride (4 x 40 mL), dried (sodium sulfate) and the solvent evaporated *in vacuo* to give a light red gum. Evaporation of excess *tert*-butoxycarbonyl azide under vacuum (1.0 mm Hg) and recrystallization of the red solid from hexanes afforded 3-*tert*-butoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXV)(0.40 g, 88%); mp, 120-121°C; ir, 1720 cm^{-1} (C=O); nmr, δ 1.50(s,9,*tert*-Bu), 6.78(d($J_{1,2}$=8Hz),1,C_1-H), 6.74-7.09 (m,5,C_4-H,C_6-C_9-H), 7.32(d($J_{1,2}$=8Hz) of d($J_{2,4}$=1.5Hz), 1,C_2-H); Exact mass calc'd for $C_{16}H_{16}N_2O_2{}^{32}S$: 300.0933; found (high resolution ms): 300.0930. Initial purification of 0.25 g of CCXXV was attempted using neutral Alumina

chromatography. Elution with methylene chloride-methanol (10:1 v/v, 200 mL) gave 10H-pyrido[3,4-b][1,4]benzothiazine (CLXXVI) as the only product.

4.15.0.0.0 3-Methoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXVI).

Diisobutylaluminum hydride (1.85 mmol, 1.85 mL of a 1.0 M solution in hexane) was added dropwise to a solution of 10-acetyl-10H-pyrido[3,4-b][1,4]benzothiazine (CCXII)(0.415 g, 1.71 mmol) in anhydrous tetrahydrofuran (20 mL) under a nitrogen atmosphere at 0°C with stirring. The red solution was allowed to stir for 1 h at 0°C and methyl chloroformate (0.53 g, 5.6 mmol) was added. The resulting red suspension was stirred at room temperature for 4 h under a positive nitrogen pressure. Water (10 mL) was added and the pH of the mixture adjusted to 9 using 1.0 N sodium hydroxide. The aqueous mixture was extracted with methylene chloride (5 x 40 mL), dried (sodium sulfate) and the solvent evaporated in vacuo to give a solid which was recrystallized from hexanes-acetone to yield 3-methoxycarbonyl-3H-pyrido[3,4-b][1,4]benzothiazine (CCXXVI)(0.395 g, 90%) as a light red powder: mp, 131-132°C; ir, 1760 cm^{-1} (C=O); nmr, δ 3.96(s,3,CH_3), 5.86(d($J_{1,2}$=8Hz),1,C_1-H), 6.73-7.16(m,5,C_4-H,C_6-C_9-H), 7.42(d($J_{1,2}$=8Hz) of d($J_{2,4}$=1.5Hz), 1,C_2-H); Exact mass calc'd for $C_{13}H_{10}N_2O_2{}^{32}S$: 258.0463; found (high resolution ms): 258.0463.

4.16.0.0.0 Analgesic testing.

A. Phenylquinone writhing test[290].

Five male ICR mice (20-25 g) were confined to their own glass jar and were denied food and water for the duration of the experiment. The test compound, dissolved in water or as a suspension in water using Tween 80 as a solubilizer, was given subcutaneously to each mouse at a dose of 0.1 mL/10 g body weight followed 30 min later by an intraperitoneal dose of 0.03% phenylbenzoquinone in 5% ethanol (0.1 mL/10 g body weight). Ten min later each mouse was counted for each writhing abdominal constriction response over a ten minute period. The average number of writhes for the five mice were compared to a similar set of mice receiving only 0.03% phenylbenzoquinone. The % change is calculated according to the following equation:

% change = 100-(number of writhes in the treated group/number of writhes in the control group) X 100.

B. Hot plate test[293,294].

Five male ICR mice (20-25 g) were individually placed on a copper hot plate maintained at temperature of 54.5°C (boiling acetone). Each mouse was timed from the moment it was placed on the hot plate till the time it showed obvious discomfort (thumping of rear leg or jumping off the hot plate surface). The mice were then given a

subcutaneous dose of the test compound (0.1 mL/10 g body weight) and 30 min later the hot plate assay was repeated. The average time of contact with the hot plate was compared before and after the dosing of the test compound. No mouse was allowed to stay on the hot plate for more than 30 sec. The % analgesia was calculated using the following equation:

$$\% \text{ analgesia} = \frac{(T_t \ -T_o)}{(T_{max}-T_o)} \times 100$$

T_o = control time; T_t = latency time at 30 min; T_{max} = 30 sec.

C. Narcotic antagonistic evaluation using the phenylquinone writhing test.

Five male ICR mice (20-25 g) were confined to their own glass jar and were denied food and water for the duration of the experiment. The narcotic antagonist, dissolved in water or as a suspension in water using Tween 80 as a solubilizer, was given subcutaneously to each mouse at a dose of 0.1 mL/10 g body weight followed 15 min later by a subcutaneous dose of the known analgesic (0.1 mL/10 g body weight). Phenylbenzoquinone (0.03%) (0.1 mL/10 g body weight) was given by intraperitoneal dose 30 min later and the duration of the experiment is as described in the phenylquinone test.

4.17.1.0.0 Antimicrobial testing.

A. Procedure for 2,7-diazabicyclo[4.1.0]hept-3-enes.

The organisms used in the study are listed in the discussion. Compounds, unless soluble in water, were dissolved in DMSO and diluted serially to various concentrations. The concentrations of stock were prepared in such a way that when 0.5 mL was added to 15 mL of agar media the desired final concentrations were obtained. The agar plates were streaked with a loopful of test organism suspension at a concentration of approximately 10^5 organisms/mL. The plates were incubated for 2-14 days for fungi at 24°C and at 35°C for bacteria. The result is expressed as minimal inhibitory concentration which was defined as the lowest concentration that prevented visible growth on the media.

B. Procedure for 1-alkylpiperidylidene-2-cyan(sulfon)amides.

The organisms used in the study are listed in the discussion. The agent dissolved in water or methanol was added by micro-pipet to a 4 mm paper disc and after drying placed on a microbial lawn. The lawn was prepared by adding 1 mL of overnight bacterial culture to 200 mL of antibiotic agar, pouring into 20 x 20 cm forms and allowing to solidify. The cultures were incubated at 37°C overnight and the zones of inhibition measured.

C. Procedure for 3-azaphenothiazine derivatives.

The organisms used in the study are listed in the discussion. Compounds were dissolved in 0.3 mL of DMSO and added to 9 mL antibiotic broth for bacteria and 9 mL sabouraud-dextrose broth for fungi to give a final concentration which was 100, 10 and 1 μg/mL respectively. The tubes were inoculated with approximately 10^5 test organism suspension. The tubes were incubated for 6 days at 37°C for bacteria and 25°C for fungi. The result is expressed as minimal inhibitory concentraton which was defined as the lowest concentration that prevented visible growth in the broth.

4.17.2.0.0 Antiprotozoal testing[317].

The test organisms used were *Trichomonas vaginalis* ATCC 30003 growing in TXM basal medium and *Entamoeba histolytica* ATCC 30015 growing in TP-S-1 monophasic medium. Each test compound was added to the liquid medium of 10 μg/mL final concentration for the amoeba and 50 μg/mL for *Trichomonas*. Each tube was then innoculated with trophozoites (10^5/mL) grown in the same medium for 48 h. The innoculated media were incubated for 24 and 48 h at 35°C. To enumerate the total population of parasites an aliquot of each test culture was diluted in saline containing formaldehyde (1%). Cell counting was performed with the aid of a Speirs-Levy eosinophil counting chamber. The result is expressed as minimal inhibitory concentraton which was taken as the

lowest concentration of each compound that inhibited 90% of growth.

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